

From: Wholley, David (FNIH) [T]
Sent: Thu, 22 Jun 2017 17:11:42 -0400
To: Collins, Francis (NIH/OD) [E]
Subject: FW: Partnership for Accelerating Cancer Therapies
Attachments: PACT Partner Briefing Deck 021017vF4.pdf, PACT Executive Summary 5-3-17.pdf, PACT_Whitepaper_032817.pdf

Just a reminder...and so you don't have to search for the note

David Wholley
Director, Research Partnerships
Foundation for the National Institutes of Health
(301) 594-6343
fnih.org

Learn more about the FNIH in our 2016 Annual Report: fnih.org/AnnualReport.

From: Collins, Francis (NIH/OD) [E]
Sent: Saturday, May 06, 2017 7:13 AM
To: [REDACTED] (b) (4), (b) (6)
Cc: Wholley, David (FNIH) [T] <dwholley@fnih.org>
Subject: Partnership for Accelerating Cancer Therapies

Dear [REDACTED] (b):
(4)

It was a pleasure to meet you at the Milken LA meeting, and I'm glad we got a chance to talk about the Partnership for Accelerating Cancer Therapies (PACT), which we have been developing with multiple pharmaceutical companies and FDA over the last eight months or so. As we discussed, PACT is focused on the critical issue of developing better biomarkers for selecting and testing cancer immunotherapies and relevant combinations. Following up your request for more information, I have attached a text executive summary and a slide deck overviewing the partnership, as well as the full text of the white paper that contains the initial research plan for those who may need more detail.

(b) (4)



All the best, Francis

Partnership for Accelerating Cancer Therapies (PACT)

Slides for Partner Briefings
February 2017



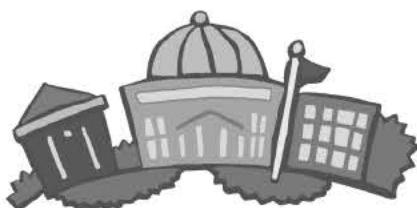
NIH - 003323

The Foundation for the National Institutes of Health (FNIH) will be the program managers for PACT

The FNIH was established by Congress in 1990 as a not-for-profit 501(c)(3) charitable organization



The Foundation began its work in **1996** to facilitate groundbreaking research at the NIH and worldwide



By creating effective alliances to advance biomedical research



501(c)(3)
Non-governmental
not-for-profit & independent
Board of Directors

More than **550**
projects supported

120+
active research partnerships,
scientific education/training,
conferences/events and
capital programs

NIH - 003324

93%

of funds directly support programs



In 2016, Charity Navigator gave FNIH a 4 star perfect score rating. The FNIH ranks in the top 1% of all organizations ranked

13 years
of outstanding
Charity Navigator ratings

Select partnerships at the FNIH

• Accelerating Medicines Partnership NIH (OD), NIA, NIAMS, NIDDK, 10 companies, 9 not-for-profit organizations	\$230 million
• Grand Challenges in Global Health (GCGH) Bill & Melinda Gates Foundation	\$201 million
• LungMAP: Master Lung Protocol Trial NCI (SWOG), FDA, Friends of Cancer Research, 5 companies to date	\$163 million
• Alzheimer's Disease Neuroimaging Initiative (ADNI) NIA, NIBIB, 25+ companies, 3 not-for-profit organizations	\$148 million
• Vector-Based Control of Transmission (VCTR) VRC/NIAID, Bill & Melinda Gates Foundation	\$78 million
• The Biomarkers Consortium <i>FDA, NIH, CMS, PhRMA, BIO, pharmaceutical and nutrition companies, not-for-profit organizations</i>	\$72 million
• Comprehensive T Cell Vaccine Immune Monitoring Consortium (CT-VIMC) Bill & Melinda Gates Foundation, NIAID	\$50 million
• MAL-ED: The Interactions of Malnutrition and Enteric Infections, Effect on Childhood Development Bill & Melinda Gates Foundation, Fogarty Institute Center (NIH)	\$46 million

TOTAL: \$984 million

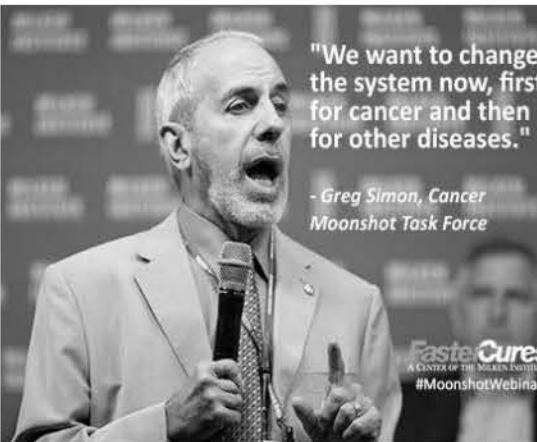
The pursuit of IO and combination therapies faces many challenges

Companies are pursuing hundreds of existing trials, yet:

- + Large number of potential combinations to be tested
 - + Lack of biomarkers to predict and understand patient outcomes
 - + Lack of robust, standardized assays
 - + Lack of reproducibility of data across trials
- = *Need to fill knowledge gaps and efficiently use research resources*

Solution: A systematic effort to develop and share biomarker and related clinical data to support clinical testing of combination therapies – PACT

PACT was developed in response to these challenges as one of the Cancer Moonshot Initiative programs



“ I plan to do two things: increase resources—both private and public—to fight cancer, and break down silos and bring all the cancer fighters together—to work together, share information, and end cancer as we know it. ”

Vice President Joseph Biden
February 2016



NIH - 003327

The design of PACT represents consensus from industry, government, and academic experts in the field

PACT is a public-private partnership being developed as part of the Cancer Moonshot effort. FNIH has led an initial research design effort over the past 6 months involving 42 scientists from NCI, FDA, and 14 companies:

- AbbVie
- Amgen
- AstraZeneca
- Bayer
- Boehringer-Ingelheim
- BMS
- EMD Serono
- Genentech
- GSK
- Lilly
- Merck
- Novartis
- Pfizer
- Takeda

- Additional support provided by PhRMA

42 scientists contributed to PACT Design Phase whitepaper

	Axel Hoos (GSK) – Industry Co-Chair	Jeff Engelman (Novartis) – Industry Co-Chair	
<u>INDUSTRY PARTICIPANTS</u>	Andrew Schade (Eli Lilly)	David Reese (Amgen)	Greg Plowman (Eli Lilly)
	Jessie English (EMD Serono)	Vicki Goodman (BMS)	Armin Schuler (EMD Serono)
	Paul Rejto (Pfizer)	Jeff Ecsedy (Takeda)	Bob Abraham (Pfizer)
	Flavio Solca (Boehringer-Ingelheim)	Jianda Yuan (Merck)	Norbert Kraut (Boehringer-Ingelheim)
	Matthew Albert (Genentech)	Carl Barrett (AstraZeneca)	Chandra Ramanathan (Bayer)
<u>GOVERNMENT PARTICIPANTS</u>	Helen Chen (NCI-CTEP) – NIH Co-Chair		Percy Ivy (NCI-CTEP) – NIH Co-Chair
	Magdalena Thurin (NCI)	Tony Kerlavage (NCI)	Lisa McShane (NCI)
	Howard Streicher (NCI)	Kevin Howcroft (NCI)	Malcolm Smith (NCI)
	Marc Theoret (FDA)	Reena Phillip (FDA)	Ke Liu (FDA)
	Rebecca Baker (NIH)		Allison Lea (NIH)
<u>ACADEMIC PARTICIPANTS</u>	Mario Sznol (Yale)	Antoni Ribas (UCLA)	Patricia LoRusso (Yale)
	Jedd Wolchok (MSKCC)	Steve Hodi (DFCI)	John Byrd (OSU)
<u>PACT PROGRAM MANAGEMENT</u>	David Wholley (FNIH)		
	Stacey Adam (FNIH)		

NIH - 003329

Two PACT program areas emerged from the Design Phase; Program Area 1 will focus on biomarker development and testing and infrastructure creation...

Program Area 1: Facilitate robust, systematic, uniformly conducted clinical testing of known and exploratory biomarkers that enable better understanding of response and resistance to IO combinations and guide treatment strategies

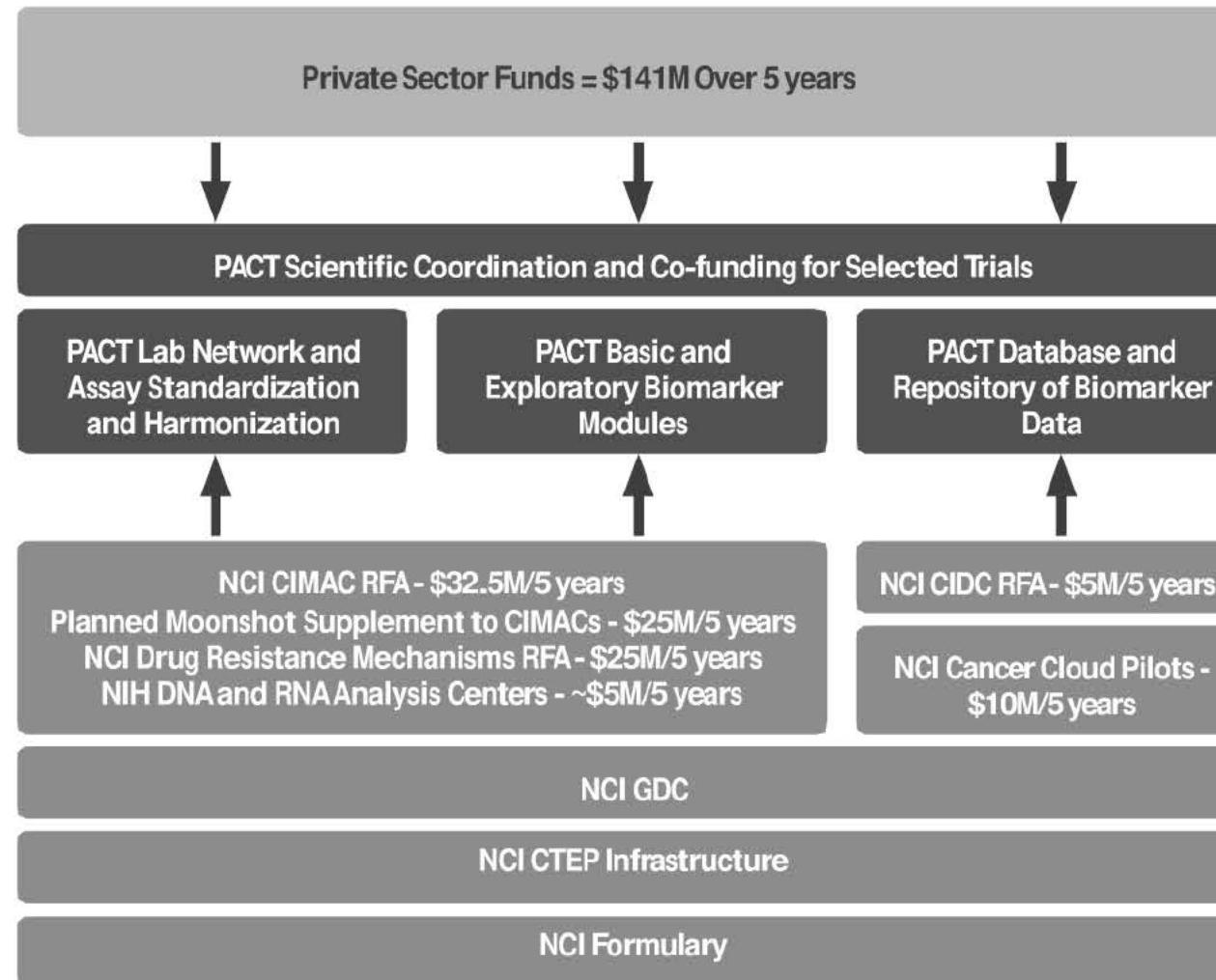
- Establish a **network of 3-5 core laboratories** to conduct, standardize, and validate biomarker assays
- Fund the **development of new exploratory biomarkers and assays** of high relevance to and impact on the field
- **Incorporate biomarker modules into trials** prioritized by PACT and coordinate their adoption broadly across the oncology research community
- Create a **comprehensive database** that integrates biomarker module and clinical data to enable pre-competitive correlative biomarker analyses

...while Program Area 2 will focus on strategic assessment of and outreach to the IO field, as well as coordination and co-funding of selected clinical trials

Program Area 2: Provide scientific coordination for the identification of clinical combination therapy trials important to the field but not already being performed elsewhere, and co-fund such trials with partners.

- Create and maintain a “**landscape analysis**” of combination therapy trials and biomarkers across the IO space, enabling categorization of prospective new trials based on relevance
- Select and **co-fund high relevance combination trials** not already being performed by other entities, leveraging existing trial networks
- **Facilitate information sharing** by all stakeholders to better coordinate clinical/translational oncology programs, **align investigative approaches**, and enable the **most relevant trials to be conducted**
- Includes active outreach to other IO research efforts on an ongoing basis

PACT will build on current and planned NCI investments: recent RFAs and existing infrastructure provide a “shovel ready” foundation for PACT



NIH - 003332

Three PACT Governance bodies will provide joint oversight – but with streamlined review procedures and policies

PACT Executive Committee
(NCI/Industry/FDA/Patient Groups)

- ▶ Strategic direction
- ▶ Resolution of policy issues
- ▶ Communication with partner leadership



PACT Joint Steering Committee
(NCI/FDA/Industry/Nonprofit)

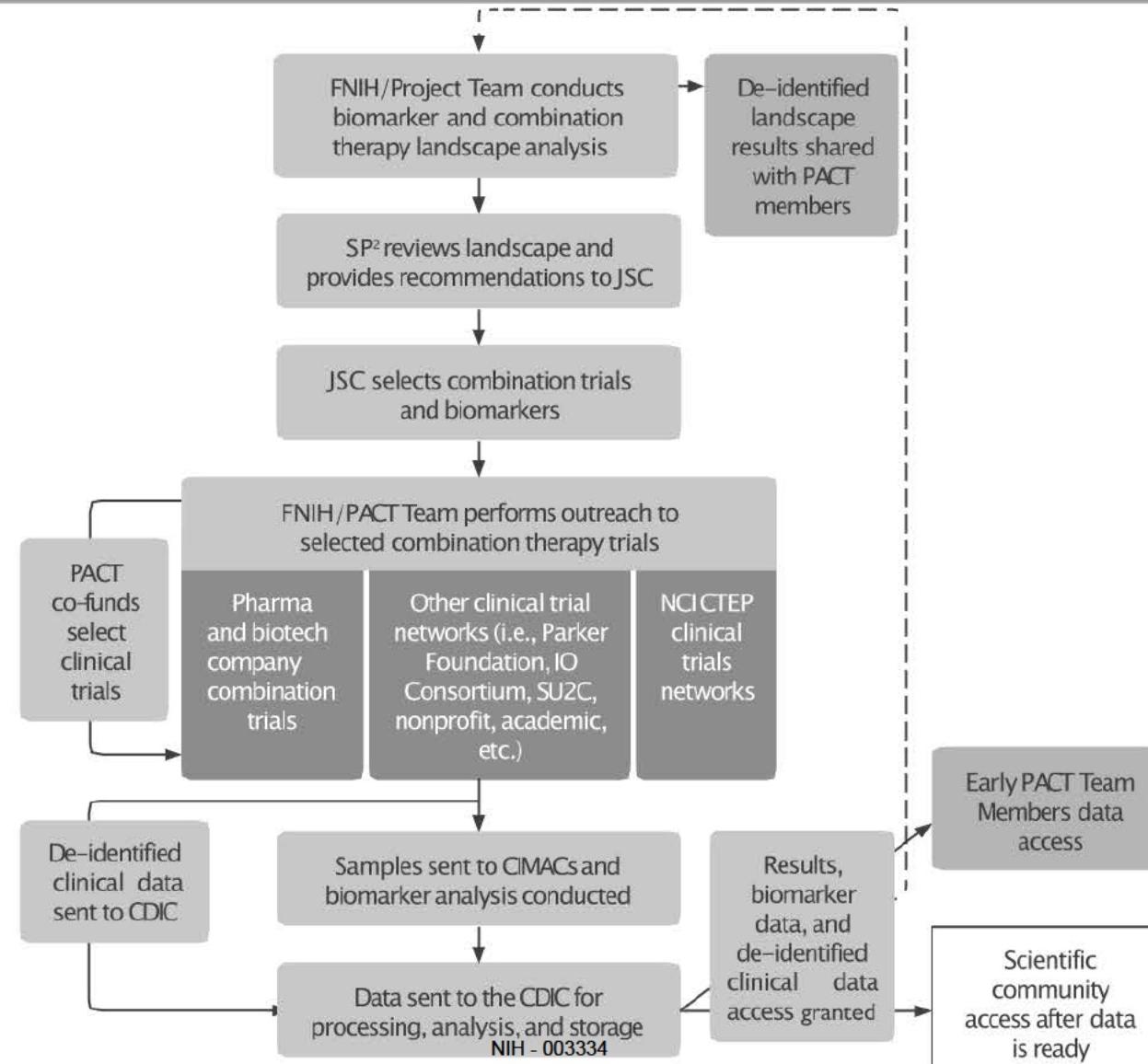
- ▶ Project funding decisions
- ▶ Operational oversight
- ▶ Milestone/plan management
- ▶ Outreach to other initiatives



PACT Scientific Project Selection Panel (SP²)
(NCI/Academic/Ex-Pharma)

- ▶ Landscape and biomarker assessments
- ▶ Project funding recommendations (advisory function only)

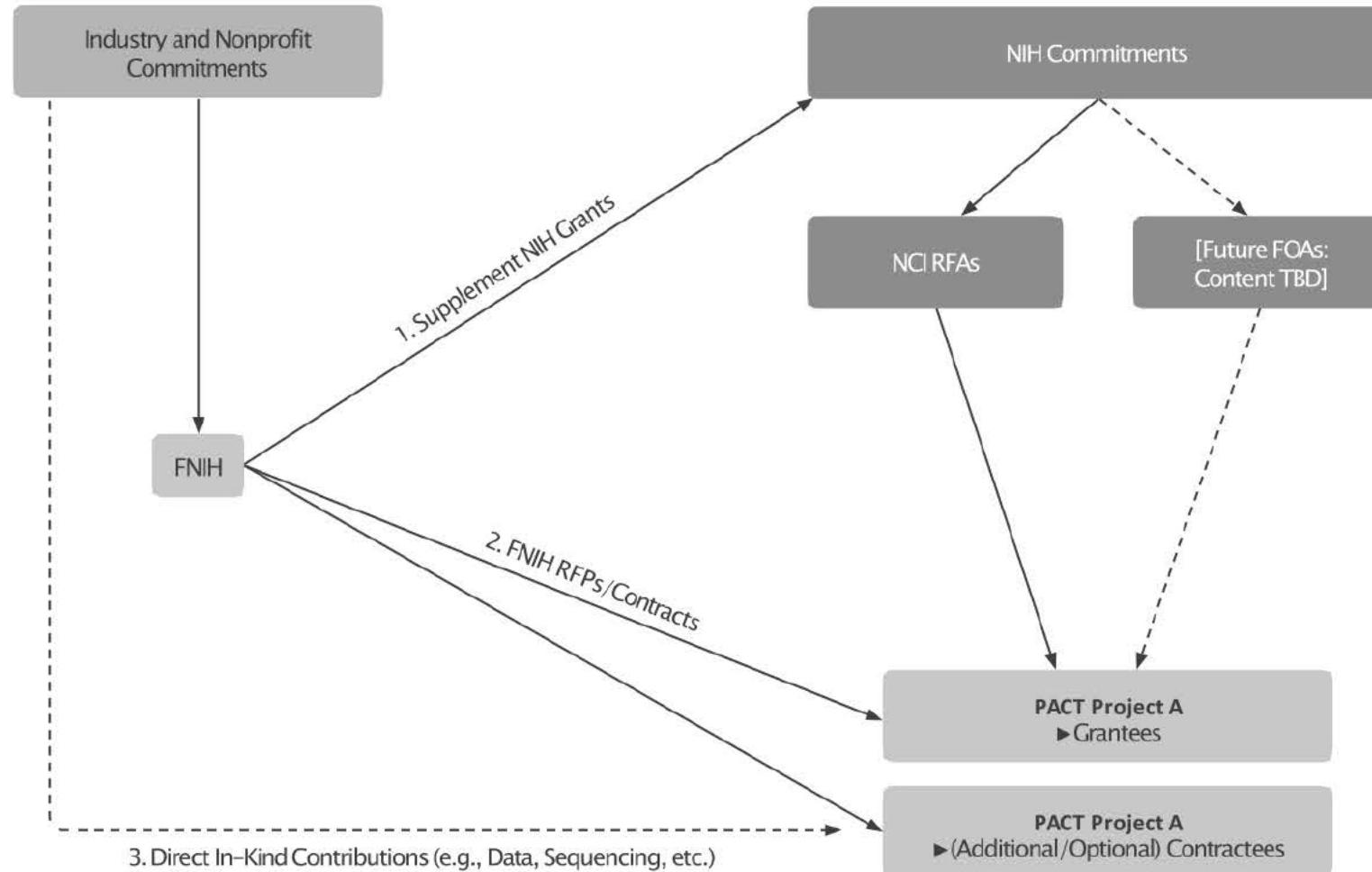
PACT offers a flexible, but efficient mechanism to develop novel markers and use them to select and test the most appropriate combination therapies



PACT will require total funding of ~\$251M over 5 years, with an investment of ~\$141M/5 years needed from the private sector

Consolidated Itemized PACT Budget		
All Costs Reflect Total Over 5 Years		
Project Plan Section	Budget Item/ Project Goal	(b) (4)
Project 1.1.1 & 1.2	Create core laboratory network to conduct biomarker assays	(b) (4)
Project 1.3	Create database to bank IO biomarker data from clinical trial	(b) (4)
Project 1.4	Standardize and harmonize biomarker assays for IO therapy	(b) (4)
Project 1.1.2	Development of new IO biomarkers	(b) (4)
Project 1.1.2 & 1.4	Expansion biorepository capabilities for sample storage	(b) (4)
Program Area 1		
Project 2.1	Conduct bi-annual landscape analysis to determine priority biomarkers and combination therapies Compensate SP ² members for trial and biomarker landscape review	(b) (4)
Project 2.2	PACT co-funding for high priority combination clinical trials	(b) (4)
Project 2.3	Outreach and coordination with other IO efforts	(b) (4)
Program Area 2		
FNIH Program Management Costs		
PACT Initiative Total		
Program Area 1 – “Buy-up” Option		\$251M
•Supplement to defray costs of tissue collection at clinical sites		
Program Area 2 – “Buy-up” Options		NIH
•Additional co-funded clinical trials		

Private sector funds for can be deployed flexibly through FNIH to PACT in a variety of ways, as required by specific project needs



The collaborative nature of PACT offers distinct—and considerable—value for its stakeholders and the oncology research community at large

- Core laboratories and database provide access to:
 - Standardized immune biomarkers modules, enabling a systematic approach across trials
 - Standardized, harmonized assay platforms, procedures, and best practices
 - Biomarker analyses to accelerate hypothesis testing
 - Clinical trial and biomarker landscape analyses
- Opportunities to initiate high relevance trials with PACT co-funding
- Data and insights to support regulatory decision-making
- More systematic approach to IO + combinations across the field
- Mechanism to share insights and resources with other Moonshot and IO collaborations

Private sector funders will have an direct voting role in further defining the PACT research plan and in PACT governing committees

The proposed PACT program also has synergies with several areas of recommendation from the Cancer Moonshot Blue Ribbon Panel

- Network for direct patient engagement ★ Potential PACT synergies
- Cancer immunotherapy translational trials network ★
- Therapeutic target identification to overcome drug resistance ★
- A national cancer data ecosystem for sharing and analysis ★
- Fusion oncoproteins in pediatric cancer
- Symptom management research
- Prevention and early detection: implementation of evidence-based approaches
- Retrospective analysis of biospecimens from patients treated with standard of care ★
- Generation of human tumor atlases ★
- Development of new enabling cancer technologies

Assuming timely success at funding PACT, we are aiming for an operational launch of the initiative in 3Q of this year

Next steps:

- Finalize PACT budget and white paper, distribute for review (February, 2017)
- Outreach to potential collaborators (patient organizations, non-profits, other companies, professional and standards organizations, etc.) (February-March, 2017)
- Partners identified and funds pledged via FNIH (March-June, 2017)
- FNIH will convene an in-person meeting with committed partners to develop detailed research plans for each project, including detailed budgets, timelines and milestones (3Q, 2017)
- Desired launch date of PACT (3Q, 2017)

NIH - 003340

Biomarkers to be Included in PACT

BASIC ASSAYS

(To be run on all patients in each trial)

- Peripheral Samples: Flow cytometry and CyTOF – 3 panels - T and B cell
- Tumor: immunohistochemistry
- Peripheral Samples: ELISA
- Whole exome sequencing (150X coverage)
- RNA-seq (150 million reads/sample)
- cfDNA (using DNA-seq)

EXPLORATORY ASSAYS

(Examples)

- Expanded flow cytometry (innate immune cell panels)
- CNVs
- SNPs
- Single cell/nuclei RNA-seq
- CTC
- T and B cell deep receptor sequencing
- cfRNA
- Microbes
- Exosomes
- Microvesicles
- Expanded immunohistochemistry
- Immunofluorescence
- Others TBD

Executive Summary

Recent advances in cancer treatment have offered the prospect of greatly enhanced outcomes, prolonged survival, and cure for some patients. Much of the recent success has been driven by the development of new immuno-oncology (IO) agents, leading to an explosion of translational research as well as investment in the field. To date, however, the improvements in outcomes and cure generated by the monotherapies of these agents are possible only for a minority of patients, and emerging data demonstrate that the greatest impact on cancer treatment will be achieved by combinations of multiple IO agents or of IO and non-IO agents. The successful pursuit of these combination therapies is complicated, however, by the sheer numbers of possible combinations, by high biologic complexity, and by the need for new translational biomarkers and assays to guide which patients should receive which combinations. These challenges are further compounded by the novelty and intensely competitive nature of the IO field, which has encouraged fragmented and at times duplicative research approaches.

To solve these challenges, a systematic cross-sector effort is required to identify and develop robust, standardized biomarkers and related clinical data that support the selection and testing of promising therapeutic combinations. The magnitude of this task and the substantial current knowledge gaps within the field make it unlikely a single stakeholder can execute such a mission alone. As a part of its support of the Cancer Moonshot, the National Institutes of Health (NIH) has proposed a 5-year, ~\$250 million precompetitive public-private research collaboration called the Partnership for Accelerating Cancer Therapies (PACT) to enable achievement of these goals. The initial strategic plan for PACT has been developed through a process led by the Foundation for the NIH (FNIH) with input from 42 key opinion leaders in the cancer field, encompassing representatives from the National Cancer Institute (NCI), U.S. Food and Drug Administration (FDA), academia, and 15 industry partners—AbbVie, Amgen, AstraZeneca, Bayer, Boehringer- Ingelheim, BMS, EMD Serono, Genentech, GSK, Lilly, Merck, Novartis, Pfizer, PhRMA, and Takeda.

PACT aims to accelerate the development of effective combination therapies by enabling critical clinical investigations not covered by others, unifying clinical biomarker investigation, filling knowledge gaps, and integrating information from multiple sources, through two programs:

Program 1: Facilitate robust, systematic, and uniformly conducted clinical testing of basic biomarkers that enable researchers and clinicians to better understand the mechanisms of response and resistance to treatment strategies. PACT will provide a systematic approach to immune and related oncology biomarker investigation in clinical trials by providing standardized biomarker modules, which can be utilized within the PACT programs and across the research community. These modules allow for (a) consistent generation of data, (b) access to uniform and harmonized assays to support data reproducibility, (c) comparability of data across trials, and (d) discovery/validation of new biomarkers for combination immunotherapies and related combinations. Specific elements of the program include the following:

- Providing a set of basic biomarker modules for uniform clinical application.
- Establishing a network of 3–5 core laboratories to coordinate, conduct, validate, and standardize biomarker assays. Funding the development of standardized biomarkers for immunoprofiling and exploratory biomarker assays of high relevance.
- Incorporating biomarkers and data collection standards into trials prioritized through PACT and coordinating their adoption broadly across the IO research community.
- Creating a comprehensive database that integrates biomarker and clinical data to enable pre-competitive correlative biomarker analyses.

Program 2: Provide scientific coordination for the selection of clinical combination therapy trials important to the field but not already being performed elsewhere, and co-fund such trials with partners. This will be accomplished by the following:

- Creating and maintaining a “landscape analysis” of combination therapy trials and biomarkers across the entire IO and oncology space, enabling categorization of prospective new trials based on relevance.
- Selecting and co-funding high relevance combination trials not being performed by other entities, while leveraging significant existing investments (such as in trial networks) made by the government, companies, and nonprofit foundations.
- Facilitating information sharing by all stakeholders to better coordinate clinical/translational oncology programs, align investigative approaches, avoid duplication of effort, share resources, and enable more relevant high-quality trials to be conducted. This will include active outreach to other IO research efforts on an ongoing basis.

The core laboratory, assay development, and database functions required as part of Program 1 will be built on a solid base of research infrastructure and academic grants funded by NCI. Fortunately, NCI has recently released several Requests for Applications (RFAs) in November 2016 that are highly germane to the core goals of PACT (see Appendix 5). Based largely on existing funding from the Precision Oncology Initiative, with additional planned Cancer Moonshot funding, these RFAs seek

applications for ~\$110 million in funding over 5 years beginning in 2017 for a number of Cancer Immune Monitoring and Analysis Centers (CIMACs), a Cancer Immunologic Data Commons (CIDC), and several related initiatives that create integrated multidisciplinary research cores with basic, translational, and computational expertise. Although currently limited as to the number of sites, assays, and data types supported, these grants provide a “shovel ready” foundation for the core lab and database functions required by PACT, particularly when combined with NCI’s recently announced Formulary initiative and its existing national clinical trials network and genomic data management programs.

In addition to supporting these resources, PACT will coordinate and standardize use of existing standardized biomarker assays to most efficiently use available resources. If available, fully validated existing biomarker assays can be conducted through parties outside PACT but channel data into the PACT database, provided assays are performed to PACT standards.

(b) (4)

A joint governance structure will maintain close involvement by all partners in key decisions, consisting of:

- An operationally focused PACT Joint Steering Committee (JSC) to direct the research plan and ensure adherence to project milestones
- A PACT Scientific Project Selection Panel (SP2) to analyze potential therapy/biomarker combinations and advise the JSC regarding fundable PACT studies
- A PACT Executive Committee (EC) to provide strategic direction, communication with partner leadership, and resolution of policy issues.

Voting participation in the JSC and EC will be split 50/50 between government and private sector partners. The SP² will consist of key academic/NCI oncology experts and scientists with industry oncology experience in drug development who lack significant financial and employment ties to individual companies in order to ensure its advisory role is carried out with objectivity and transparency.

All PACT data will be released publicly as promptly and broadly as possible in keeping with NIH’s mission and policy, though also dependent on restrictions in underlying clinical trial and grant agreements. Where feasible, PACT participants will have early access to data, but consistent with these restrictions.

The value proposition for PACT stakeholders, for the oncology field, and for patients will be considerable, providing immediate:

- Access to standardized immune biomarker modules, enabling a systematic and uniform analytical approach across trials
- Access to databases of pre-competitive biomarker analyses, accelerating hypothesis testing and decision-making
- Access to core facilities with standardized analysis platforms, procedures, and best practices, working with regulatory agencies to ensure the highest quality evidence and documentation, relevant to potential registration and labeling
- Access to clinical trial landscape analyses for combination therapies and biomarkers across the entire IO space, and the opportunity to align research priorities, avoid duplication of effort, fill gaps, and share resources
- Opportunities to initiate high relevance trials with company assets for PACT co-funding
- Opportunity to drive new collaborations resulting from PACT insights and contribute to improving cure rates for patients under the goals of the Cancer Moonshot Initiative

(b) (4)

Once key partners are confirmed, FNIH will reconvene the scientific leads from committed partners to develop a final research plan, including detailed project plans and go/no-go milestones. Given the sense of urgency in addressing patient needs, the timing of NIH funding, and the rapid pace of progress in the field, formal launch of PACT is being targeted for Q3 of 2017.

Partnership for Accelerating Cancer Therapies (PACT)

FINAL DESIGN WHITEPAPER - FEBRUARY 2017



National Institutes
of Health

NIH - 003344



Foundation for the
National Institutes of Health

PACT Design Phase Sponsors

AbbVie, Inc.

Amgen, Inc.

AstraZeneca

Bayer AG

Boehringer-Ingelheim GmbH

Bristol-Myers Squibb

EMD Serono, Inc.

Genentech, Inc.

GlaxoSmithKline

Eli Lilly

Merck Sharp & Dohme Corp.

Novartis Pharmaceuticals

Pfizer, Inc.

Pharmaceutical Research and Manufacturers of America

Takeda Pharmaceutical Company Ltd

National Institutes of Health/National Cancer Institute

U.S. Food and Drug Administration

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Executive Summary

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- ▶ Creating a comprehensive database that integrates biomarker and clinical data to enable pre-competitive correlative biomarker analyses.

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- ▶ Selecting and co-funding high relevance combination trials not being performed by other entities, while leveraging significant existing investments (such as in trial networks) made by the government, companies, and nonprofit foundations.
- ▶ Facilitating information sharing by all stakeholders to better coordinate clinical/translational oncology programs, align investigative approaches, avoid duplication of effort, share resources, and enable more relevant high-quality trials to be conducted. This will include active outreach to other IO research efforts on an ongoing basis.

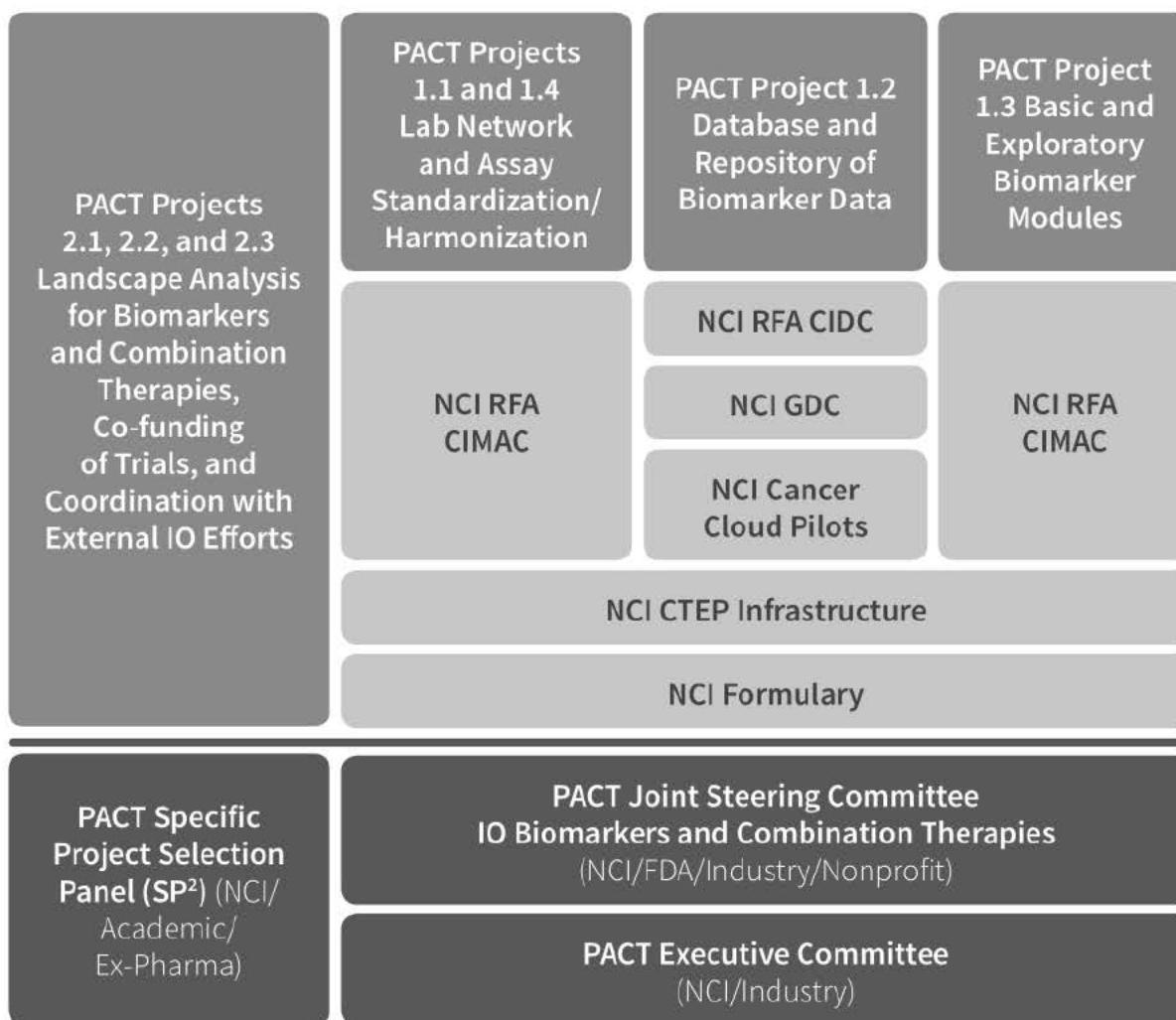
The core laboratory, assay development, and database functions required as part of Program 1 will be built on a solid base of research infrastructure and academic grants funded by NCI. Fortunately, NCI has recently released several Requests for Applications (RFAs) in November 2016 that are highly germane to the core goals of PACT (see **Appendix 5**). Based largely on existing funding from the Precision Oncology Initiative, with additional planned Cancer Moonshot funding, these RFAs seek applications for ~\$110 million in funding over 5 years beginning in 2017 for a number of Cancer Immune Monitoring and Analysis Centers (CIMACs), a Cancer Immunologic Data Commons (CIDC), and several related initiatives that create integrated multidisciplinary research cores with basic, translational, and computational expertise. Although currently limited as to the number of sites, assays, and data types supported, these grants provide a “shovel ready” foundation for the core lab and database functions required by PACT, particularly when combined with NCI’s recently announced Formulary initiative and its existing national clinical trials network and genomic data management programs.

In addition to supporting these resources, PACT will coordinate and standardize use of existing standardized biomarker assays to most efficiently use available resources. If available, fully validated existing biomarker assays can be conducted through parties outside PACT but channel data into the PACT database, provided assays are performed to PACT standards.

The additional ~\$141 million/5 years required to meet the baseline PACT goals will be raised through FNIH. A majority of these funds will be used to supplement NCI grants, although funds may be disbursed directly through FNIH contracts where appropriate. Additional funds may be sought later for future projects of interest to further PACT partnerships and goals.

A joint governance structure will maintain close involvement by all partners in key decisions, consisting of:

- ▶ An operationally focused PACT Joint Steering Committee (JSC) to direct the research plan and ensure adherence to project milestones
- ▶ A PACT Scientific Project Selection Panel (SP²) to analyze potential therapy/biomarker combinations and advise the JSC regarding fundable PACT studies
- ▶ A PACT Executive Committee (EC) to provide strategic direction, communication with partner leadership, and resolution of policy issues.



- FNIH Managed Private Sector Raised Funds
- NIH Managed Funds
- Governance Bodies

Voting participation in the JSC and EC will be split 50/50 between government and private sector partners. The SP² will consist of key academic/NCI oncology experts and scientists with industry oncology experience in drug development who lack significant financial and employment ties to individual companies in order to ensure its advisory role is carried out with objectivity and transparency.

All PACT data will be released publicly as promptly and broadly as possible in keeping with NIH's mission and policy, though also dependent on restrictions in underlying clinical trial and grant agreements. Where feasible, PACT participants will have early access to data; however, data will be retained for analysis and not released publically until study analysis is complete and closed to accrual and treatment in concert with our research agreements for a reasonable time.

The **value proposition** for PACT stakeholders, for the oncology field, and for patients will be considerable, providing immediate:

- ▶ Access to standardized immune biomarker modules, enabling a systematic and uniform analytical approach across trials
- ▶ Access to databases of pre-competitive biomarker analyses, accelerating hypothesis testing and decision-making
- ▶ Access to core facilities with standardized analysis platforms, procedures, and best practices, working with regulatory agencies to ensure the highest quality evidence and documentation, relevant to potential registration and labeling
- ▶ Access to clinical trial landscape analyses for combination therapies and biomarkers across the entire IO space, and the opportunity to align research priorities, avoid duplication of effort, fill gaps, and share resources
- ▶ Opportunities to initiate high relevance trials with company assets for PACT co-funding
- ▶ Opportunity to drive new collaborations resulting from PACT insights and contribute to improving cure rates for patients under the goals of the Cancer Moonshot Initiative

(b) (4)

Introduction

Over the last decade, cancer treatment options have substantially improved, now offering the prospect of greatly enhanced outcomes prolonged survival or cure for some patients. To date, such outcomes are only possible for a minority of patients; however, there is significant potential to expand this benefit to a broad majority of patients in many cancers.

Recently, the positive clinical outcomes associated with progress in cancer treatments have largely been driven by IO agents, which stimulate the immune system to eradicate or control cancer cells. The success of IO therapies in the treatment of melanoma, renal cell carcinoma, NSCLC, as well as some rare tumors such as Merckle cell tumors and Hodgkin's lymphoma has led to a rapid explosion of investments in IO research by the pharmaceutical industry, academic institutions, government, and nonprofit organizations. IO's greatest impact on cancer treatment is expected from combination therapies involving both multiple IO and complementary non-IO agents and will require systematic investigation of a large spectrum of new agents across the portfolio boundaries of individual companies. Despite the great resources invested in IO and related combination regimens to date, the task is complicated by high biologic complexity, the need for translational biomarkers to direct therapy, and the deeply competitive nature of the field, which has led to some redundant research and development efforts, duplication of costs and resources, and the absence of systematic approaches to scientific investigation.

To achieve the desired improvement in outcomes for a majority of patients, a systematic effort across a complex spectrum of pharmaceutical, biotech, academic, government and nonprofit stakeholders is required to effectively test therapeutic combination options and identify biologic markers that direct the right treatment combination to the right patient. This idea has long been gaining followers in the IO field and potential methods for addressing it have been laid out by key scientists in the field (Hoos, Britten, Huber, & O'Donnell-Tormey, 2011). However, the magnitude of this task and the substantial knowledge gaps that still exist make it unlikely that any single stakeholder can execute the task alone. A public-private research partnership such as PACT offers a unique opportunity to address this challenge by coordinating resources across NIH, FDA, biopharmaceutical companies, and patient groups using a focused, collaborative approach. PACT aims to accelerate progress toward improved outcomes by facilitating and enabling critical investigations not covered by others, thus filling knowledge gaps and integrating information from multiple sources across the cancer research sphere.

PACT will establish two program areas that will help determine high priority combination therapies and biomarkers (to be tested by PACT and others in the IO field) and generate the knowledge needed to reduce the number of unnecessary combination trials and improve patient participation in such trials.

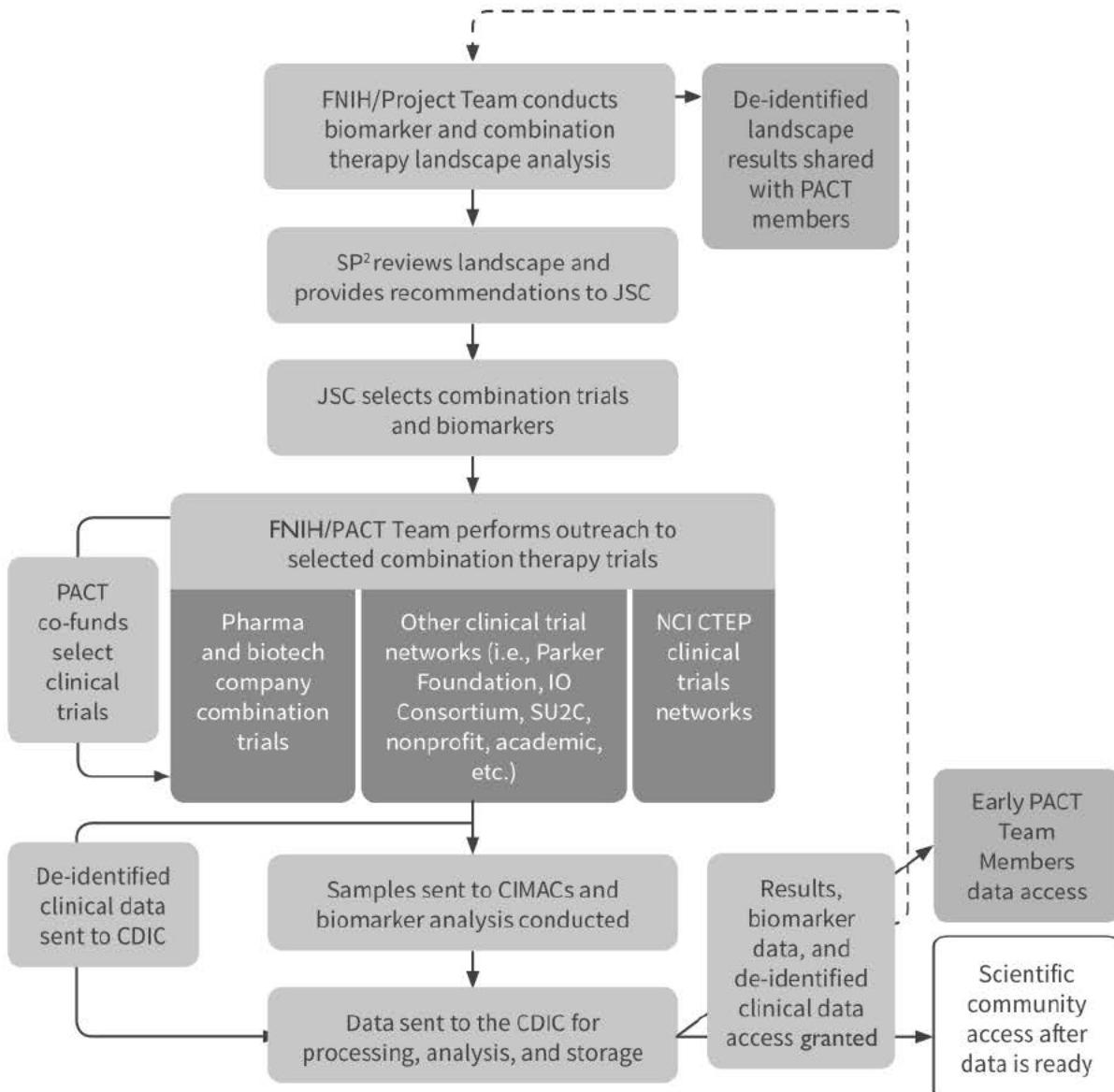
Program Area 1 will facilitate robust, systematic, and uniformly conducted clinical testing of basic biomarkers that enable researchers and clinicians to better understand the mechanisms of response and resistance to treatment strategies. PACT will provide a systematic approach to

immune and related oncology biomarker investigation in clinical trials by providing standardized biomarker modules, which can be utilized within the PACT programs and across the research community. These modules allow for (a) consistent generation of data, (b) access to uniform and harmonized assays to support data reproducibility, (c) comparability of data across trials, and (d) discovery/validation of new biomarkers for combination immunotherapies and related combinations. Specific elements of the program include the following:

- ▶ Providing standardized biomarker modules for uniform clinical application across the community.
- ▶ Establishing a network of 3–5 core laboratories to coordinate, conduct, validate, and standardize biomarker assays and data collection standards.
- ▶ Funding the development of standardized biomarkers for immunoprofiling and exploratory biomarker assays of high relevance.
- ▶ Incorporating biomarkers into trials prioritized through PACT and coordinating their adoption broadly across the IO research community.
- ▶ Creating a comprehensive database that integrates biomarker and clinical data to enable pre-competitive correlative biomarker analyses.

Program Area 2 will provide scientific coordination for the selection of clinical combination therapy trials important to oncology but not already being performed elsewhere, and co-fund a carefully selected subset of such trials with partners. This will be accomplished by the following:

- ▶ Creating and maintaining a “landscape analysis” of combination therapy trials and biomarkers across the entire IO space, enabling categorization of prospective new trials based on relevance.
- ▶ Selecting and co-funding high relevance combination trials not being performed by other entities, while leveraging significant existing investments (such as trial networks) made by the government, companies, and nonprofit foundations.
- ▶ Facilitating information sharing by all stakeholders to better coordinate clinical/translational oncology programs, align investigative approaches, avoid duplication of effort, share resources, and enable more relevant high-quality trials to be conducted. This will include active outreach to other IO research efforts on an ongoing basis.



Value Proposition

The value proposition for participating stakeholders in PACT will be considerable:

- ▶ Access to an infrastructure for incorporating standardized immune biomarker modules in clinical trials, enabling a systematic analysis approach across trials, with reproducible assay results, reduced costs and resources, and enhanced power of correlative analysis
- ▶ Access to core facilities with standardized analysis platforms, procedures, and best practices, working with regulatory agencies to ensure the highest quality evidence and documentation, also relevant to potential registration and labeling
- ▶ Access to a comprehensive database for pre-competitive correlative biomarker analyses, accelerating data acquisition and hypothesis testing, and enhancing decision-making
- ▶ Enhanced reliability and speed of clinically relevant biomarker identification for identifying patients who will benefit from specific immunotherapy agents or combinations
- ▶ Opportunity to be the first to initiate a high relevance trial with the company's asset of interest, co-funded by PACT or its partners (e.g. NCI)
- ▶ Access to and participation in the coordination of clinical and translational programs across organizations in the IO space (pharmaceutical companies, biotech, academia, government, and nonprofits) to align investigative approaches, avoid duplication of effort, share/preserve resources, and thus allow for more relevant trials to be conducted
- ▶ Access to and participation in the creation of an up-to-date clinical trial landscape analysis for combination therapies across the entire IO space, including access to information about relevant investigations not yet covered by any party.
- ▶ Contributing to the goal of the U.S. Cancer Moonshot Initiative of doubling the rate of progress in cancer research and delivering more cures to patients
- ▶ Opportunity to drive new collaborations resulting from the insights of the PACT partnership

Program Area 1: Facilitate robust, systematic, and uniformly conducted clinical testing of basic biomarkers that enable researchers and clinicians to better understand the mechanisms of response and resistance to treatment strategies

Objective

To reach the next level of benefit of immunotherapy for a broader number of patients, it is necessary to understand and characterize the complexity and dynamics of the immune state in cancer patients and the therapeutically induced changes in immune profiles in the tumor and the periphery.

Experimental findings point to the value of biomarkers for cancer immunotherapy in predicting benefit of therapy and understanding the mechanisms of resistance. For example, high tumor expression of PD-L1 is predictive of increased likelihood of clinical benefit from anti-PD-1 monotherapy in patients with NSCLC. Other factors associated with response include high mutational load, inflammatory gene signatures, and tumor-infiltrating lymphocytes. More recently, tumor genomic studies in patients treated with checkpoint inhibitors have revealed mutations in interferon response pathway genes as a potential mechanism of primary or acquired resistance. While these results are promising, systematic testing in larger patient cohorts is needed to confirm preliminary analyses and clinically validate predictive biomarker candidates.

PACT will provide the foundation for harmonizing the use of biomarker assays, data collection, and data banking, as well as optimize systematic biomarker incorporation into clinical trials to understand response and resistance to cancer immunotherapies and to enable new treatment strategies. Specifically, projects under Program Area 1 will address a few key challenges: inconsistent analytical validation standards and assay methodologies across trials, limited power of individual trials, and lack of common data platforms for combined analysis and cross validation across trials. Project 1.1 lays out the biomarkers the PACT team proposes to systematically incorporate into clinical trials as standard practice, while Projects 1.2, 1.3, and 1.4 detail the infrastructure that will be established to evaluate these proposed biomarkers in clinical trials.

Project 1.1—Establishing biomarker modules for systematic and uniform biomarker testing in clinical trials (for PACT and non-PACT studies)

Challenge/Opportunity

The lack of validated biomarkers and the current inability to compare data between clinical trials is a major challenge and partly driven by the absence of uniform and systematic biomarker investigation. This also limits the selection of the most appropriate immunotherapy regimen (single agent or combination therapy) for a given cancer patient based on validated markers. The fundamental lack of understanding of mechanistic interplay between the tumor and human immune system is a major hurdle for patient selection in IO/oncology clinical trials. Lack of data sets that encompass the molecular characterization of the tumor microenvironment (TME) correlated with clinical outcomes needs to be evaluated in appropriately sized patient data sets with a well-defined statistical analysis plan. Moreover, pharmacodynamic biomarkers can provide an early understanding about performance of a new agent or new combination, accelerating decision-making and prioritization. Comparable data sets from most trials conducted by stakeholders in the community, which close data gaps and allow for more systematic analyses, are needed to build validated biomarkers and truly effective patient selection strategies.

Solution

The PACT initiative will select biomarkers that are relevant to the testing of IO agents in clinical trials and that will help researchers to understand key biologic processes and to optimize decision-making in the application of existing and novel therapeutics. Biomarkers will be grouped in “modules”, a set of studies or analyses built around specific biological topics or areas of inquiry (for example, immune cell biology or liquid biopsies). Modules will fall into two categories: basic and exploratory.

Basic modules address commonly used or known biomarkers which can be reliably tested by a broad spectrum of clinical trials. They are fundamental to investigating specific aspects of cancer biology and building baseline data for how immunotherapy treatments effect this biology, have current clinical utility, and should be executable by the majority of trial sponsors in the oncology field. Basic modules must be usable by a majority of investigators. They are meant to be broadly applicable to most trials and still deliver insights for specific trials.

Exploratory modules will test novel or less well-established markers), and represent an expansion into new areas of science or technology which need further validation or which PACT participants may not be positioned to (or not desire to) study on their own. They are meant to address a specific biology question of interest relevant to each specific trial. Exploratory modules can be added to PACT on an optional basis until enough evidence consistently demonstrates their relevance and applicability so that they can be considered basic standard biomarkers. The exploratory biomarker modules will accommodate new scientific and biomarker discoveries and advances to be introduced and tested by a few investigators initially. Exploratory biomarkers

can cover all types of new assays being developed for tracking treatment response, including imaging, sequencing, proteomics, immunohistochemistry (IHC) multiplexing, and single-cell analysis.

Modules are expected to be used as follows:

1. All PACT-associated studies will be required to test PACT basic biomarker modules—i.e., meaning each study participating in PACT will need to run the basic modules.
2. NCI will adopt PACT biomarker module recommendations for all NCI studies whenever feasible. These efforts will be synergized with the assays being selected for the CIMAC laboratory network.
3. PACT partners and collaborators will be asked to use PACT selected biomarkers with the aim to standardize and harmonize data generation and collection in studies outside of PACT. The use of these biomarkers can either be through the use of the CIMACs or through use of standardized protocols. The process of selecting these non-PACT, external trials to use the CIMACs will be facilitated through the Scientific Project Selection Panel (SP²) and the Joint Steering Committee (JSC).

Each basic biomarker module will employ comparable methods across all participating medical centers and trials. Such comparability will require selection of assays with similar specifications and harmonization of the assays used across participating centers. If achieved, this will allow the cross comparison and coordinated analysis of data across multiple trials.

In addition, the PACT initiative will need to identify clinical trials from which standard biomarkers and/or samples can be collected that can be used to characterize or validate novel Exploratory biomarkers. PACT will place emphasis on identifying combination therapy clinical trials where collecting biomarker information is a high priority to the IO community. The understanding of the mechanisms of response and resistance to IO therapies that will result from the biomarker analyses will aid in the further refinement and selection of combination therapies for future testing.

PACT will not establish its own clinical trials network infrastructure or fully sponsor trials itself, but will partner with and utilize existing clinical trials networks, such as the NCI's National Clinical Trials Network (NCTN) and Experimental Therapeutics Clinical Trials Network (ETCTN), or networks established by nonprofit organizations or industry sponsors. The SP² will identify these trials based on the periodic landscape analyses that will be conducted as part of PACT and pass their recommendations to the JSC. The JSC and the PACT outreach team can work with these external networks or sponsors to help broker a partnership with PACT on those trials resulting in eventual deposition of the relevant biomarker and clinical data into the common PACT database. PACT will also consider providing supplementary funding to conduct these trials in selected cases. This process for trial selection is further described below in **Program Area 2**.

Focus of the Project

As described above, two types of biomarker “modules” will be pursued for PACT: basic and exploratory modules. Table 1 describes the modules defined thus far by the PACT Working Groups. This table is divided by basic and exploratory modules and defines what tissue collection will be necessary for each.

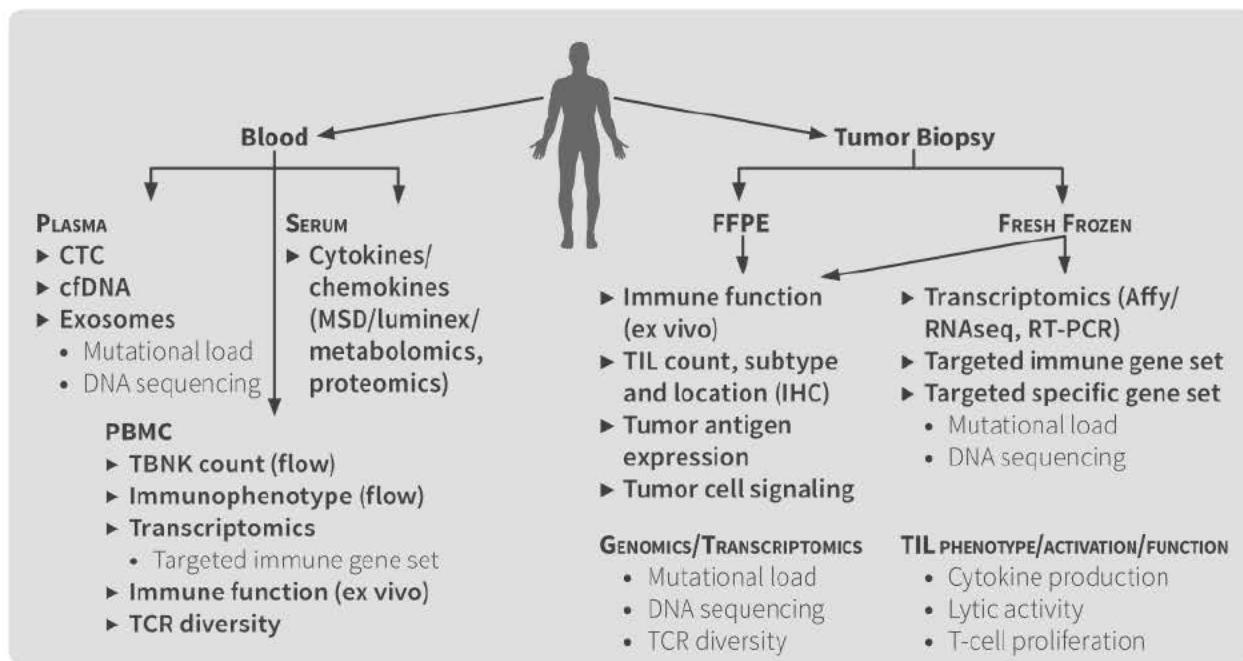
TABLE 1. PROPOSED PACT BIOMARKER MODULES

MODULE #	BIOLOGY TO BE STUDIED	DESIRED ASSAYS	SAMPLE REQUIREMENT
BASIC			
1A	Immune cell biology	Periphery: Flow cytometry and CyTOF—3 (T and B cell panels) Tumor: IHC	Blood, tumor biopsies (core and bulk)
1B	Peripheral cytokines/chemokines	ELISA	Blood/serum
2A	Cancer genetics / somatic mutations	Whole exome sequencing (100X coverage—per standard practice)	Tumor biopsies (core and bulk), blood—isolated DNA 200-500 ng
3A	Transcriptomics of the tumor microenvironment	RNA-seq (150 million reads/sample)	Tumor biopsies (core and bulk), blood
4A	Liquid biopsy	cfDNA assay	Blood—Streck or EDTA tube
EXPLORATORY			
1C	Immune cell biology	Expanded flow cytometry (innate immune cell panels)	Tumor biopsies (core and bulk), blood
2B	Cancer genetics / somatic mutations	CNVs, SNPs, T and B cell deep receptor sequencing	Tumor biopsies (core and bulk), blood
3B	Transcriptomics of the tumor microenvironment	Single cell/nuclei RNA seq, others TBD	Tumor biopsies—single cell isolates, blood
4B	Liquid biopsy	CTC, cfRNA, exosomes, microvesicles, others	Blood—collection tubes TBD
5	Defining the microbiome	Microbes and others (see section below)	Stool, saliva, others TBD
6	Non-immune tumor architecture	IHC, IF, others TBD	Tumor biopsies (core and bulk)

Basic biomarkers will be standard and mandatory for all PACT biomarker analyses, subject to the sample collection limitations for each trial; exploratory biomarkers will be optional. Biomarkers selected for the basic modules will be harmonized with the assays and platforms named in the CIMAC RFAs. The PACT team has established the priority ranking for mandatory modules: 1a > 2a > 4a > 3a > 1b. Exploratory modules can be conducted at the discretion of PIs; however, if these modules are run, the data generated should be captured in the PACT database. The consistent acquisition of such data across all PACT-related studies will constitute a major advance.

Common Tissue Collection Needs for Biomarker Modules

Any biomarker investigation is only as good as the quality of human samples collected and the reproducibility of the assays used. PACT intends to address both of these issues through careful collection and standardization of biomarker assays. An initial schema for biomarker testing has been outlined as follows:



Baseline Tumor, During Treatment, and Post Treatment (When Possible):

- ▶ Bulk tumor resection (fresh)
- ▶ Core biopsy materials
- ▶ Blood
 - ▶ Standardized whole blood and plasma collection (optional banking protocol)
 - ▶ EDTA tubes, Red top serum tubes, CPT tubes with sodium heparin, and others
- ▶ Bone marrow for hematologic malignancies

- ▶ Standard tissue processing procedures
 - ▷ FFPE
 - ▷ Snap frozen—referred for DNA extraction
 - ▷ RNAlater
 - ▷ Single cell suspension
 - Tissue process with or without enzyme digestion
 - Cell freezing media and standard operation procedure
- ▶ Standard operating procedures (SOP) for dual extraction of DNA and RNA if possible should be explored
 - ▷ Isolated DNA necessary for samples for WES—200–500 ng
- ▶ Emerging tissue processing approaches
 - ▷ Single nuclei recovery for RNA-seq
 - ▷ Smart Tube system for flow cytometry (<http://smarttubeinc.com/index.htm>)
- ▶ Potential biomaterials for microbiome sampling
 - ▷ Serum
 - ▷ Mucosal (Oral swabs, endoscope)
 - ▷ Urine/Fecal
 - ▷ Tumor

Tissue Collection

It is anticipated that tissue collection including blood draws, biopsies and other specimen collections could cost up to \$5,000/patient/time point, if specimen processing is included in the estimated costs. The PACT team anticipates this cost will likely be covered by the groups sponsoring the trials, and that PACT would support the actual conduct of the biomarker assays in the CIMAC laboratories. As a potential optional incentive for trials to participate in PACT, the PACT team could choose to subsidize this cost for trial sites; however, this would need to be a buy-up option, and PACT would likely not be able to support the full \$5,000. This is therefore listed in the budget as a buy-up option at \$7.5 million over 5 years.

Establishing a Biospecimen Repository

Establishing a biospecimen repository will be necessary to allow for easier centralized storage, processing, and accessioning of samples for those trials where further biomarker assays maybe required or desired in the future. This will be especially critical for PBMCs, cfDNA, and other liquid biopsy assays, where a given trial may want to store samples for batch runs or for development of future assays and technologies. Two clear models for biobanking could be established: 1) decentralized sample collection, with centralized storage, and centralized database/informatics and 2) decentralized sample collection, with decentralized storage, and centralized

informatics. PACT proposes to follow the second model, since PACT trials will be run by multiple organizations, and there will likely be a need to allow the industry trials to retain possession of samples from the trials that they exclusively fund but use PACT biomarker modules or PACT core laboratories. However, PACT will, where possible, recommend that centralized storage also take place.

One option for utilizing existing infrastructure for centralized storage would be to use existing biospecimen repositories at NCI. Both the NCTN and the ETCTN already have biorepositories, and private funding could be used to supplement the grants that already sponsor these repositories. Regardless of where the specimens are stored, the PACT effort will require a centralized accessioning of the samples for initial processing before being sent to the CIMACs for processing. This will allow for accurate tracking of all biospecimens that are part of the PACT effort and could potentially be used for future testing.

Biospecimen Repository Expansion Budget

Supplementing the existing biospecimen repositories at NCI will likely cost ~\$1 million to \$2 million per year to process, accession, and store the samples for the potential 720+ patient samples that are currently due to be collected as part of the CIMACs or external trials. This number would increase if the number of patients were to scale up. This means that a total of as much as \$10 million over 5 years would be necessary for this effort. If PACT were to establish an independently run biorepository, the cost would likely be much greater than this amount. Therefore, \$10 million dollars over 5 years has been added to the PACT budget estimate (see the table at the end of this section.)

1.1.1—Basic Modules

The PACT team had proposed that IHC/flow cytometry (depending on tumor type) and DNA sequencing should be the top priority modules. RNA-seq should be a second priority, unless a particular study mandates a need for this assay. These core modules were selected by the PACT team because they provide a solid knowledge base for cross-comparison of clinical trials that are testing IO therapies. In addition, these modules are well developed and offer good options for standardized assay platforms, as well as analysis techniques. However, a common platform for each module will still need to be selected as part the research plan for this project for PACT. Platforms and analysis techniques will be selected by the JSC in consultation with the CIMAC team.

Focus of the Project

Mandatory biomarkers will be prioritized by tissue availability and trial needs, but the mandatory modules run for PACT will be standardized across all trials. This means that for some trials not all modules will be used, so PACT has ranked the assays based on amounts of tissue (see above).

Biomarker Module 1: Immune Biology

Focus of the Project

Module 1 is organized into two categories of focus: peripheral samples (i.e., circulating soluble or cell-based biomarkers) and tumor samples. Samples of peripheral blood and resection or biopsy of tumor tissue will be collected, and broad testing is planned.

Module 1a: Immune Cell Biology

Peripheral Specimens

Peripheral samples of blood, serum, or plasma should be collected at multiple time points throughout the course of treatment to allow for longitudinal evaluation of changes in immune biology and, if possible, to correspond with measures of drug exposure. These time points and sample sizes will be dictated by individual clinical protocols. Assays for characterizing the functionality of immune cells by in vitro stimulation can also be developed and will constitute the third flow cytometry panel for Module 1a basic biomarkers.

To analyze peripheral samples, the most common technologies used are flow cytometry and CyTOF for cell based analyses and ELISA-based methodologies for measurement of soluble markers. For a basic evaluation of immune cell biology in the periphery, the panels listed below in Table 2 are recommended. In addition, markers of functional characterization of isolated PBMCs are shown.

TABLE 2. T CELL MARKER PANELS BY FLOW CYTOMETRY

ACTIVATION	EXHAUSTION	FUNCTIONAL
LIVE OR DEAD	LIVE OR DEAD	LIVE OR DEAD
CD3	CD3	CD3
CD4	CD4	CD4
CD8	CD8	CD8
CD45RO	CD45RO	IFNg
CD69	LAG3	TNF α
ICOS	TIM3	GZMB
OX40	CD161	IL-2
FOXP3		
CD127		

In Vitro Functional Characterization of PBMCs
 ► Ag recall
 ► Epitope spreading
 ► MLRs

Tumor

Obtaining multiple samples of tumor tissue must be attempted throughout the course of a patient's treatment to allow for longitudinal evaluation of immune response depending upon the needs of the protocol.

Tissues will be collected by resection and/or biopsy. These samples can be fixed, frozen, or used immediately for IHC, gene expression, and TIL analyses (by flow cytometry). Similarly, TILs, once isolated and if sufficient, can be used for in vitro stimulations for cytokine analyses. Specific protocols for sample collection and assay execution are to be defined. For the IHC-based assays, standardized quantitative imaging analysis methodologies will be developed. For flow cytometry-based assays, standardized methods for cell gating will be employed. Tissue is less readily available at multiple sampling points and will be prioritized for use in testing for biomarkers. Evaluation by multiplex IHC will take precedence over flow cytometry and in vitro analyses of immune function, as the recovery of isolated TILs from biopsies may not be sufficient. An example basic panel for IHC is shown in Table 3.

TABLE 3. MARKERS (IHC)

CD3	CD16	PD1
CD8	CD56	MHC-1
CD45RO	CD19	TIM3
CD4	CD68	LAG3
FOXP3		

Value Proposition

Data from this module will add to the overall information to understand mechanisms of action for the intervention, mechanisms of therapeutic sensitivity and resistance, and patient selection leading to efficacy.

Approximate Module Budget

Periphery: This estimate is based on a six panel flow analysis, including a measure of receptor occupancy, which should be ~\$2,500–\$3,000/sample. However, this cost may be reduced if we are able to use bulk rates and synergized cost structures within the CIMACs network.

Tumor: This estimate is based on using a simple or single biomarker IHC approach. It should be noted that this approach uses the most tissue.

The cost for this analysis will be ~\$250–\$300/marker. The total cost for the panel is approximately \$3,250–\$3,900/sample. An alternative approach will be to generate multicolor IHC panels that will lead to less utilization of tumor tissue and may provide a moderate cost improvement.

Module 1b: Cytokines/Chemokines Periphery

Multiplex cytokine evaluations using one of the several ELISA-based platforms, such as Mesoscale, ELISA, or Luminex, will be used to test several circulating cytokines in the plasma/serum. The markers will include mediators of immune activation, inflammation, target cell killing, and safety signals such as those of the cytokine release syndrome shown in Table 4.

TABLE 4. SOLUBLE FACTORS

G-CSF	IL17	GZMA
GM-CSF	IL2	GZMB
IFN γ	IL4	PERFORIN
IL1	IL6	CCL2
IL10	CXCL2	CCL3
IL12	IL7	CCL8
IL13	M-CSF	CCL5
IL15	TGF β	CX3CL1
IL16	TNF α	CXCL10 (IP-10)
IL21		CXCL9 (MIG)

Multiplex Immunoassays

- ▶ Immune activation
 - Cytokines
 - Chemokines
 - Inflammatory mediators
- ▶ Safety
 - CRS-targeted panel

Approximate Module Budget

This estimate is based on a 29-panel multiplex ELISA-based platform which will be ~\$500-\$600/sample, depending on the choice of platform.

Module 2a: Cancer Genetics/Somatic Mutations

Advances in genome sequencing technologies at affordable cost along with progress in bioinformatics has propelled the field of somatic cancer genetics into a new era. The exponential growth of cancer genome datasets has been justified as a means to identify new cancer genes and pathways that could be the basis for molecular classification of tumors, initiate novel target-based drug discovery programs, and perform molecular profiling of tumors to match therapies with patient-specific genetic alterations. The relevance of mutated antigens in the field of tumor immunology (Gilboa, 1999) has been corroborated by studies of patients receiving checkpoint inhibitors that reported significant clinical benefits correlating with mutational and neoantigen loads (Miao & Van Allen, 2016; Rizvi et al., 2015; Snyder et al., 2014). In addition, tumors with a large number of somatic mutations due to mismatch-repair defects have been shown to be susceptible to immune checkpoint PD-1 blockade therapy (Le et al., 2015). The basis for this correlation is that an increased number of mutations will increase the number of neoantigen specific T-cells capable of eliciting a strong immunogenic response; the very checkpoint blockade that impedes the tumor's ability to suppress neighboring T-cells results in an increase in tumor-cell killing in the presence of a highly immunogenic tumor.

Focus of the Project

To continue to expand on this somatic mutation knowledge and assure that it can be leveraged to determine novel genetic biomarkers related to immunotherapy, the PACT team proposed to conduct whole exome sequencing (WES), taking into account the following principles.

Matched normal tissue: In order to ascertain whether a sequence variant found in a tumor is somatic or germline, it is necessary to sequence normal DNA from the same individual. While tumor-only WES data can be compared to large germline databases to infer whether a mutation is somatic, false positive calls are frequent, particularly in ethnic populations (Garofalo et al., 2016).

Sequence coverage: Mutation load and predicted neoantigens have rapidly emerged as standard biomarkers used in IO trials. The current gold standard laboratory assay for measuring mutation and neoantigen load is whole exome sequencing (WES; n = ~20,000 genes), as opposed to whole genome sequencing (WGS) that provides additional information regarding noncoding somatic mutations that do not produce neoantigens. WES is therefore more cost-effective for immune-oncology purposes. Given that clinical genomics laboratories that are hospital-based or commercial more commonly use gene panels that cover dozens to hundreds of genes, questions have arisen whether these could be adequate for immunotherapy purposes. Dr. Garofalo and colleagues performed comparisons of gene panels with WES. Mutation loads were estimated using large (n=300–500) gene panels and were shown to correlate with WES mutational load above a certain cutoff, although by virtue of the limited sampling of human genes contained in gene panels, the vast majority of neoantigens could not be detected. Therefore, it may be concluded that gene panels are substantially inferior to WES in predicting neoantigens (Garofalo et al., 2016). For cost efficiency purposes, PACT will infer trunk versus branch mutations via allelic frequencies from a single tumor site versus multiple tumor sections.

Mutation calling: A recommended approach in the context of multicenter and multiyear clinical studies is to store raw NGS data files in secure databases and reanalyze all data simultaneously using a validated and harmonized pipeline to allow robust analyses of mutation and neoantigen loads with clinical and other data.

Copy number alterations (CNAs): CNAs, which include gains and deletions of DNA segments, can be detected using clinical WES (Rennert et al., 2016). While the relevance of CNAs in predicting the efficacy of immunotherapies is generally less understood, there are reports of specific CNAs correlating with immune phenotypes, and it will be informative to correlate CNAs with other immune markers.

Neoepitope prediction algorithms: Combined use of multiple tools likely gives a better prediction; however, more efforts are needed to accurately assess the immunoprotective properties of neoepitopes.

Approximate Module Budget

This estimate is based on analyzing both tumor and normal samples from each patient.

The WES assay cost is \$500–\$1,100/sample (100x coverage, depending on the number of GB). The cost per patient may be estimated at \$2,200 if one assumes 100x WES with 9 GB. The PACT JSC will need to select the optimal coverage to cost ratio that will be acceptable for the WES Basic biomarker module.

Module 3a: Transcriptomic Characterization of Microenvironment

Transcriptional programs in the tumor microenvironment are an important downstream marker of biological processes such as T-cell activation with reported gene expression profile (GEP) signatures including Type I interferon, interferon gamma, T-cell exhaustion, Th1, as well as the cytolytic activity score. Signatures of extrinsic immune suppression such as IDO-1 or TGF-beta expression highlight mechanisms in addition to immune checkpoint blockade that may overcome resistance through combination therapy. In addition to signatures in tumor, pharmacodynamic changes in immune gene expression signatures in blood have been shown to correlate with response to treatment. Approaches to measure mRNA expression span low complexity techniques including qRT-PCR as well as medium complexity technologies such as TaqMan, Nanostring, Luminex, and targeted NGS panels via hybridization capture or PCR amplification, as well as genome-wide RNA sequencing. Several GEP signatures predictive of patient response to treatment have been reported: NanoString signatures in tumor have correlated with clinical outcome in patients treated with PD-1 blockade (Cesano, 2015; Geiss et al., 2008; Man Chow et al., 2016; Piha-Paul et al., 2016; Ribas et al., 2015). Whole transcriptome profiling provides the opportunity for genome-wide characterization of the TME.

Focus of the Project

The PACT team proposes to perform systematic RNA-seq at a depth of 150 million reads across all tumor samples.

In addition to profiling the primary tumor prior to treatment, profiling samples during treatment or upon relapse provides insight into mechanisms of resistance, and point to attractive combination opportunities; it is therefore suggested for those tumor indications where sequential biopsies are possible.

Value Proposition

Transcriptional read-outs of individual malignant and nonmalignant cells from tumor tissue may offer additional insights into cellular states and programs (and heterogeneity therein) that may influence response or resistance to cancer immunotherapies/combinations.

Through supervised or unsupervised learning, GEP modules can be identified and correlated with important clinical outcomes such as prognosis or response to treatment. There are ongoing clinical trials using NanoString GEP signature prospectively to triage patients for different immunotherapies. Novel genes that are co-expressed with established gene expression

signatures can identify new targets and illuminate unknown biology. Fingerprinting approaches can be used to deconvolute immune subpopulations. The expression of candidate neoepitopes can be investigated, as well as effects on alternative splicing.

Approximate Module Budget

The cost of these assays range from ~\$1,000–\$3,000, depending on the platform used for sequencing, the depth of coverage requested, and the type of RNA to be analyzed. Depending on the sequencing facilities and the number of samples to be analyzed, the average cost for a 150 million read standard RNA-seq should be approximately \$1,500/sample. This would make the estimated cost/patient ~\$1,500.

Module 4a: Liquid Biopsy - cfDNA

The difficulty in acquiring routine tissue biopsies in the solid tumor setting hinders the ability of a clinical laboratory to provide real-time information to clinicians and convenient options for patients. Advances across multiple areas—sample preparation, next generation qPCR and sequencing capabilities, rare cell detection and analysis, ultra-sensitive protein detection, storing, accessing, and analyzing very large data sets—are enabling unprecedented multi-dimensional data collection. Liquid biopsy for solid tumors is currently being used, but the complexity of integrating data across cfDNA, exosomes (includes profiling mRNA, miRNA, lncRNA, proteins, etc.), and circulating tumor cells poses a challenge to exploit the full potential of this approach. Moreover, advances in liquid biopsy technologies are occurring much more rapidly than clinical validation of these assays.

Focus of the Project

Biomarkers will be driven by the clinical questions asked. While it is not realistic to propose all possible clinical settings, it is highly likely that immunotherapies will continue to be combined with other targeted agents and therefore biomarker testing will reflect the combined mechanisms of action of all agents. For instance, in nonsmall cell lung cancer, EGFR mutations and ALK fusions will still be tested even as immune-related biomarkers are adopted. For this module, we are proposing a common approach in the pre-analytical phase of testing that will allow for better comparison of analytical testing platforms chosen by individual research teams.

NGS-DNA-seq will be the primary experimental screening platform, which is good for biomarker discovery/research, LDT approaches, and is also the preferred technology in specific settings (e.g., detection of minimal residual disease in certain heme malignancies).

Value Proposition

Testing specimens derived from relevant body fluids (e.g., blood, CSF, pleural fluid, etc.) that may reflect various aspects of tumor pathobiology could better enable clinical decision-making and provide for surrogate endpoints. It could also allow for broader immunoprofiling of patients at more time points before and after IO therapy. This ability to track data from IO treated patients longitudinally and more frequently will allow for more rapid development of novel IO-related biomarkers for treatment development and efficacy. PACT proposes as its basic biomarker module for liquid biopsy to conduct mutation analysis in cfDNA. Specimens for this assay and

other liquid biopsy options can be banked in a biospecimen repository for future processing. Again, this can provide for greater ability to immunoprofile patients using assays developed in the future.

Approximate Module Budget

The cost of this assay will be determined by the cost to collect and process the cfDNA, as well as the costs for the NGS-DNA-seq. The appropriate depth of coverage will need to be selected based on the clinical needs. A safe estimate may be ~\$1,100/sample to align with the WES costs from the DNA module. However, costs could be higher depending on the sequencing coverage required to find the desired mutations in the low amount of DNA present in these samples. The appropriate cost to coverage ratio will need to be determined by the JSC.

Value Proposition for the Basic Modules

Selecting a set of high importance, broadly applicable, and widely testable biomarkers that can be conducted for every PACT-related clinical trial will allow for the systematic cross comparison of IO therapy trial data on a much grander scale than is currently possible. This will allow novel precompetitive predictive biomarkers to be developed for IO therapies of various classes. The ability to cross-compare trials will also allow for complex modeling studies to be conducted to aid in the prediction of better therapy combinations. There are several key questions in the advancement of IO therapies that the biomarkers proposed by this initiative can attempt to answer. These include target engagement, pharmacodynamic activity, mechanisms of sensitivity and/or resistance, as well as identifying the most appropriate patients to treat based on risk/benefit criteria with individual agents or combination therapies. The value of having the data from all of these standardized assays for multiple clinical trials will be to accelerate the discovery of new immunoprofiling markers that can be used to hasten the approval for novel therapies.

Approximate Budget for Basic Modules

The current cost estimations for all the Basic biomarkers, including 3 peripheral flow panels, 1–2 basic IHC assays, WES, and RNA-seq for each patient, range from \$10,000–\$14,000 per time point. (Note: this is greater than the current estimated cost per patient for the CIMACs testing, which is ~\$8,000–\$10,000/sample.)

1.1.2 - Exploratory Module/Assay Development (Buy-up Options)

Evaluation of exploratory biomarkers may also be performed depending on availability of samples from the periphery and tissue and the specific objectives of the relevant clinical trial. Various stakeholders (e.g., NCI or a company sponsor) can choose to fund these modules based on specific trial objectives or shared objectives across multiple studies. Importantly, exploratory biomarkers or novel assays are necessary for the continued evolution of the biomarker space and can graduate to become part of basic modules once better established. The proposed areas for exploratory marker development are listed below and described in detail in **Appendix 1**.

- ▶ Module 1c: Immune Cell Biology
- ▶ Module 2b: Cancer Genetics/Somatic Mutations

- ▶ Module 3b: Transcriptomic Characterization of Microenvironment
- ▶ Module 4b: Liquid Biopsy—CTC, cfRNA, exosomes
- ▶ Module 5: Defining the role of the microbiome in modulating CI responses
- ▶ Module 6: Non-Immune Cell Characterization of Tumor Microenvironment (differentiation, stroma, vasculature, etc.)

Value Proposition for the Exploratory Modules

Allowing expansion assays to be options for buy-ups for the PACT initiative will allow both the NCI and private sector to fund the development of additional assays that can then be validated to become basic modules that can be incorporated into future clinical trials. This will allow PACT to drive innovation of new IO biomarker development and allow end users to weigh in which biomarkers which markers should be developed. The value of executing these modules through PACT lies in the breadth of use of the markers that can be achieved across the community and the ability to generate consistent data in every trial. The PACT JSC can select and fund desired modules using an RFA or RFP process that insures buy-in and participation of both PACT partners and external trial sponsors.

Approximate Project Budget for the Exploratory Modules

The cost for these expansion modules will of course depend on which assays are selected to be developed and tested. The assay cost will depend the current maturity of the technology, the biomarkers to be developed, and the expense to fully test and validate them. The PACT team estimates an RFA for new biomarker development in clinical trials would cost ~\$1 million to \$2 million per biomarker, which would account for collection of enough data to analytically validate a new biomarker and potentially harmonize it to any existing data if necessary. Assuming development of each assay cost the maximum \$2 million, PACT would hope to fund development of at least one biomarker per year over 5 years for an estimated total of \$10 million for the RFA.

Project 1.2 — Creating a core laboratory network for biomarker analysis

Challenge/Opportunity

Although diagnostic tools have significantly enhanced the depth and comprehensiveness of our abilities to characterize the tumor immune microenvironment, the current use and development of translational biomarkers are limited by insufficient resources for large-scale studies, variabilities in pre-analytic/analytic qualities and standards, and, more importantly, by a lack of common standards and platforms for biomarker data collection (especially for nongenomic “immune” parameters) and inadequate computational tools/platforms for complex, high dimensional analysis.

Consequently, at least three elements are critical to enabling optimized biomarker strategies:

- ▶ Access to biospecimens from early and late stage single agent and combination clinical trials that involve relevant immunotherapy agents
- ▶ Access to laboratory resources and assays with analytical validation and standardization appropriate for achieve clinical biomarker testing
- ▶ Availability of suitable, interoperable data repositories for clinical, genomic, and non-genomic data generated across disparate trials and organizations, similar to that provided by the NCI Genomic Data Commons

Solution

PACT proposes to build on the Research Funding Announcement (RFA) released by the National Cancer Institute (NCI) in November, 2016, to establish a **network of Cancer Immune Monitoring and Analysis Centers (CIMACs) and a Cancer Immunologic Data Commons (CIDC)**, in order to provide consistent, standardized biomarker assays and data repository for NCI's extramural clinical trial networks (links to RFAs in **Appendix 5**). The RFA is open to application from academia, nonprofit and for-profit organizations, and up to 3 CIMACs will be funded with a total budget of \$32.5 million for all 3 centers from NCI over 5 years starting 2017. Each CIMAC will encompass a multidisciplinary group capable of a wide range of analyses for genomic, phenotypic, and functional characterization of the tumor immune system using analytically validated and standardized platforms. The CIMAC-CIDC network will function in a coordinated manner through a central Core Laboratory Coordination (CLC) Committee. The capacity of the proposed CIMACs will provide the mechanism and basic infrastructure needed for objectives of **Program Area 1** of the PACT initiative.

- ▶ The CIMACs to be established through the RFA are budgeted to address the biomarker study needs of early clinical trials of immunotherapy that use the NCI clinical trial networks. PACT has the potential to leverage components of this infrastructure for PACT-prioritized studies. For example, PACT can add new capacity for specific assay platforms or expand the scope of biomarker work for more clinical trials and patients selected by PACT.
- ▶ The clinical trials for PACT-supported biomarker studies can be conducted through a variety of existing clinical trial infrastructures supported by NCI, academia, nonprofits, and industry.
 - ▷ For example, the NCI Cancer Therapy Evaluation Program (CTEP) has an extensive extramural clinical trial network for phase 0 to phase IV trials [including ETCTN, NCTN, the Cancer Immunotherapy Network (CITN) and the Children's Oncology Group (COG)]. CTEP provides standing support for centralized regulatory, data collection, drug distribution infrastructures, and clinical trial conduct in the network sites. CTEP also has a large portfolio of immunotherapy and targeted agents under its collaborative agreements with multiple pharmaceutical companies. Since 2010, CTEP has initiated more than 90 phase I to phase III trials for immunotherapy agents and novel combinations involving immunotherapy.
 - ▷ Other clinical trial mechanisms would also be appropriate for PACT-supported biomarker studies, such as academia, nonprofit funded immunotherapy consortia, and industry-sponsored trial networks.

- ▶ Private sector diagnostic and assay companies and laboratories will be eligible to compete to conduct certain assays for the CIMACs if the CLC determines that this is the most efficient way to conduct these tests.
- ▶ PACT will identify existing/planned trials or develop new trials using existing trial mechanisms and support the implementation of biomarker studies in order to address important scientific questions prioritized by the PACT JSC (as described in Project 2.1 and PACT Governance).
- ▶ PACT will facilitate and maintain close communication with industry, academia, and non-profits for their inputs in identifying opportunities and gaps, prioritizing scientific projects, and sharing expertise and resources where appropriate. This effort is delineated in Project 2.2, described below.

Focus of the Project

To support the goals of the proposed PACT Program Area 1, a network of reference labs will be identified for high priority assay platforms. These “core” biomarkers to be applied are described in Project 1.1. Depending on the stages of development of specific markers and the anticipated purposes of their uses in trials, varying degrees of analytical validation will be required (defined in Project 1.4).

Proposed services for biomarker studies may include quantitative and qualitative methods for immunoprofiling using phenotyping, functional analysis, genomics, epigenomics, transcriptomic, proteomics, metabolomics, or glycomics. Although Clinical Laboratory Improvement Amendment (CLIA)-certified assays are not required for all biomarker studies to be supported by PACT, the selected core laboratories should have the capacity to carry on validation steps from analytical to clinical validation for candidate markers and perform integral biomarker assays (for treatment eligibility) in a CLIA-compliant laboratory that may require an Investigational Device Exemption (IDE) from the FDA. Assay platforms to be employed by reference labs may include, but are not limited to:

- ▶ Multi-spectral flow cytometry, mass cytometry and imaging cytometry
- ▶ DNA-seq for genotyping of variants, T-cell clonality, relevance of T-cell and B-cell epitopes
- ▶ High-throughput transcriptional profiling, RT-PCR, NanoString, RNA-seq
- ▶ Pathological and morphological imaging techniques (e.g., confocal microscopy)
- ▶ Immunohistochemistry (IHC), multiplexed immunofluorescence

The scientific goals of the lab network are to search for patient/treatment selection markers and provide mechanistic insights into immunotherapy agents and combinations. In appropriately selected clinical trials, specific biomarker objectives may include, but are not limited to:

- ▶ Defining the role of inflammation and tumor microenvironment in response/resistance
- ▶ Phenotypic and functional characterization of the immune system, and its impact on response/resistance

- ▶ Functional genomics of tumor and host
- ▶ Identifying tumor target antigens, such as neoantigen, and responding host T-cell receptor repertoire
- ▶ Developing assays to guide rational selection of combinations in individual patients
- ▶ Longitudinal sampling to monitor dynamic changes and target modulation by drug (e.g., in combination therapy)
- ▶ Defining the role/impact of the human microbiome on response/resistance
- ▶ Exploring the mechanisms and predictive markers of immune-related toxicities

A few guiding principles will be followed in the selection of the reference laboratories:

1. The network of laboratories should have the collective capabilities to carry out comprehensive immune profiling assays and analysis on clinical specimens. Based on the current understanding of relevant biomarker platforms, core and exploratory immune biomarker modules are described in Project 1.1, although the lists of the two categories may evolve with time.
2. Depending on the stage of scientific and technical development, some markers will be best tested in individual labs (such as markers utilizing newly developed technologies, and exploratory biomarkers). Others will be developed within a network of qualified labs (such as markers with existing standards and harmonization, and basic biomarkers) or a single high-capacity facility (for certain selected platforms and markers, including both basic and exploratory biomarkers).
3. Each reference lab should participate in, and agree to, the following assay validation and delivery standards:
 - ▶ Adherence to key performance metrics (to be defined) including data quality management systems; development and provision of standardized IO assays using standardized protocols and methods; and banking, tracking, and distribution of biological samples in a compliant manner that would allow dissemination to clinical practice
 - ▶ Delivery of data in standardized formats, for example, in:
 - ▶ IHC: e.g., intensity scores, percent tumor cells at each intensity, H-score, special locations
 - ▶ Next Generation Sequencing (NGS): e.g., BAM files, VCFs
 - ▶ Other scoring methods/algorithms: e.g., immune cell infiltration patterns
 - ▶ Routine, regular performance reviews focused on quality, proficiency testing, and compliance

Value Proposition

The establishment of a network of reference labs will enhance the efficacy, quality, and power of biomarker analysis across immunotherapy trials. By applying standardized sample processing and assay protocols, deviation of test results due to pre-analytical and analytical variations will be minimized, allowing for cross-trial comparisons. Systematic incorporation of key biomarker modules will expand the power of individual trials through combined analysis with other trials.

Approximate Project Budget

The estimate costs for this project is based on the NCI budget for CIMACs, as well as the PACT basic biomarker cost estimates:



The PACT funds raised to synergize with the CIMACs effort from NCI will:

- ▶ Cover the expenses of the PACT-initiated biomarker projects within PACT selected trials.
- ▶ Expand the testing services of the existing CIMAC network formed from NCI funding to establish assays for biomarker studies in trials prioritized by PACT.
- ▶ Add new assays or platforms to existing capacities.
- ▶ Add new labs with specialized capabilities of novel technologies or expand the general capabilities of the network.

Project 1.3 – Creating a database for all PACT biomarker data

Challenge/Opportunity

A pre-competitive common database or data access platform is particularly important for immunotherapy biomarkers, since individual trials, even large Phase III trials, may not have sufficient power for complex correlative analysis. However, there currently is no widely available repository that contains biomarker data for IO; instead multiple databases are being implemented without coordination and therefore without consistency. Because IO biomarker research is a nascent field, there is a huge opportunity to ensure early data harmonization

and standardization optimization. The definition, collection, storage, and sharing of data and metadata from multiple sources must be standardized: reproducibility of research results and the ability to broadly translate findings will be impossible without such standardization. The data types to be collected, and the adoption or creation of open standards for storing them need to be determined.

Solution

NCI and NIH already have programs to establish unified data repositories that enable data sharing across cancer genomic studies and that are made accessible to the scientific community, such as the Genomics Data Commons (GDC). Construction of both an Imaging Data Commons and a Proteomics Data Commons is also actively proceeding. An NCI Cancer Immunologic Data Commons (CIDC) is in the planning stages and is a natural extension of this concept, and the timing of this effort aligns well with the PACT initiative. Analysis will need to be performed to determine the appropriate model for such a repository, e.g., whether it makes more sense to create a single database to which contributors send their data, or to use a federated model, where researchers can access, combine, and analyze the data as it is acquired from multiple sources. Once a model is defined, collection mechanisms will be created to ensure the data are obtained in a fashion that does not require double or duplicative data entry. This resource will also need to have the capability to house or access corresponding patient level clinical data, i.e. diagnosis, key demographics, treatment history, and outcome history. This feature will be absolutely critical in order to make the resulting biomarker information truly useful.

Another key component for the PACT database will be that contribution of data will be mandatory for all NCI led trials; however, it is understood that for company-driven trials, participating may be limited by the presence of proprietary information. Company sponsors would therefore be allowed to limit the outcome data placed in the repository as necessary. A staged approach will be needed for implementation.

There are multiple NCI programs that have potential relevance to this Project 1.3:

- ▶ **NCI programs where large amounts of relevant data are being collected** already exist and can be leveraged for PACT.
- ▶ CTEP supported Clinical Trial Networks (as mentioned in Project 1.1). The NCI provides significant resources to the CTEP infrastructure. The NCTN grants a total of approximately \$150 million/year for trials, and the ETCTN grants a total of approximately \$20 million/year for trials. In addition, NCI also issues support contracts (CTSU, CIRB, etc.) for both total that total approximately \$60 million/year. In short, this means that during the first 5 years of PACT, the NCI will invest~\$1.1 billion/5 years or ~\$230 million/year to conduct clinical trials. Many of these trials are currently studying IO agents or combinations with IO agents. Data generated from some CTEP trials may be used for standardization and harmonization and serve as the initial population of the CDIC.

- ▷ The Quantum Immuno-oncology Lifelong Trial (QUILT) is developing a Master Protocol, and the blanket consent can be adopted to allow the data generated to be broadly shared.
- ▷ The NCI Center of Excellence in Immunology's (CEI) mission is to foster discovery, development, and delivery of novel immunologic approaches for the prevention and treatment of cancer and cancer-associated viral diseases. The CEI collaborates with the CITN, partners with the Society for the Immunotherapy of Cancer (SITC), and fosters collaborations with Biotech and Pharma.
- ▶ **NCI and private sector efforts to develop platforms for immunological data deposition, integration and/or analysis will help guide the CDIC design efforts.**
 - ▷ NCI has an initiative to establish a CIDC (a U24 mechanism RFA is in the planning stages), which would serve as a bioinformatics core center for research data collection, analyses, integration, and data sharing for studies completed by the CIMACs. This effort can be leveraged as the starting point/prototype for the Immunological Data Commons as well as for the data generated by the CIMACs. The short-term goal for this project is to collect and integrate data to allow within- and cross-trial analyses for NCI network studies. The longer-term goal is to provide a common platform to make the data accessible by the IO community and to allow integration with data from outside the NCI. This platform could be used to create common analysis pipelines, as has been done in the GDC for genomic data.
 - ▷ Platforms already exist for various data types or data integration (within industry, nonprofits, data/diagnostic companies, and academia). One example is ImmPORT, The Immunology Database and Analysis Portal, a partnership between researchers at the University of California-San Francisco, Stanford University, the University of Buffalo, the Technion-Israel Institute of Technology, and Northrop Grumman. It is funded by NIAID. ImmPORT can serve as a model for data integration.

Potential synergies between other ongoing efforts and PACT can be used to enhance both programs.

- ▶ Public/private partnerships, which can be leveraged to gain momentum and agreement on issues including the development and use of data standards, data sharing agreements, and the actual sharing of data that is being generated.
 - ▷ Global Immunotherapy Coalition (GIC)
 - ▷ Parker Institute for Cancer Immunotherapy
 - ▷ Bloomberg-Kimmel Institute for Cancer Immunotherapy

- ▶ Complementary projects, where efforts can be made to integrate with varied types of data (genomic, clinical, proteomic, imaging) and to accelerate the discovery and the development of new treatments
 - ▷ NCI Genomic Data Commons & Cancer Genomics Cloud Pilots—focused on genomics data harmonization and accessibility and analysis
 - ▷ NCI Imaging Data Commons (early-stage planning)—focused on imaging data harmonization and accessibility
 - ▷ NCI Proteomics Data Commons (early-stage planning)—focused on proteomics data harmonization and accessibility
- ▶ Other agencies
 - ▷ FDA development of standards for submissions of immunological biomarker data and related documentation designed to support potential regulatory marketing authorization, if applicable
- ▶ Standards development organizations
 - ▷ Clinical Data Interchange Standards Consortium (CDISC), including possible use of Study Data Tabulation Model (SDTM)
 - ▷ NCI Metadata Thesaurus and Cancer Data Standards Repository (caDSR)
 - ▷ Biomedical Research Integrated Domain Group (BRIDG), which is part of ISO
- ▶ Clinical trials conducted by other networks and companies
 - ▷ External trials may not utilize the same assays and platform as PACT studies but would still be useful to include in the database if there was sufficient information about the biomarkers employed to determine analytical validity.
 - ▷ Bridging or compatibility studies would need to be conducted for these trials, and data harmonization would need to be done. These tasks have been accounted for in the budget for this project.

Focus of the Project

Project 1.3 will:

- ▶ Develop a database platform —a “data commons”—that includes both published and unpublished data, to enable data sharing.
 - ▷ Selection of a database technology will need to account for the inchoate nature of this work, providing flexibility and mechanisms to standardize, store, integrate, and interrogate new types of data that will be generated. Clinical, safety, and biomarker data should be contained or accessible through one source. As much as possible, data to be collected should be defined up-front, with the understanding new data types will follow.

- ▶ Identify or enhance data collection tools for the types of biomarker data collected from the basic and expansion biomarker modules defined in Project 1.1, while concurrently developing new tools and data collection standards that may be needed for certain data platforms.
- ▶ The biomarker data platforms will likely include tumor genomics, T-cell receptor sequencing, RNA-seq and NanoString, IHC or multiplex IF, flow cytometry, cytokine panels, and functional analysis.
- ▶ As available, additional patient-level data will be included in the database to be paired with the biomarker data, such as diagnosis (e.g. cancer site, histology, staging), patient demographics (e.g. age, gender, race), treatment (e.g. medications, start / stop dates), and outcome history (vital status, disease status, relevant ancillary medications).
- ▶ Provide or develop tools to access and analyze the data and mechanisms to inform clinicians and basic and translational researchers of the challenges of drug combinations and how to optimize treatment for patients.
- ▶ Identify software to support data collection from participating institutions and integration of that data into the data commons.
 - ▶ Role-based security that takes into account HIPAA and FISMA requirements and a variety of authorization models must be an integral part of the system.
- ▶ Identify barriers to data sharing/transparency amongst various drug development parties and develop strategies to overcome those barriers.

Value Proposition

The goal of this project is to create a means to collate, maintain, harmonize, share, and curate the IO data collected in PACT-participating clinical trials, as well as any basic and translational research data that the PACT initiative may identify and request to be contributed to the database, such as that from PACT Program Area 2. The Cancer Moonshot Blue Ribbon panel has specifically called for a “national infrastructure” as a core component of the CITN, and that success will be measured by new, effective treatments “in more patients, across many different cancers.” Achieving this goal requires the ability to integrate and analyze multiple data types from a wide variety of sources. In addition to providing an IO biomarker database for the initial set of clinical trials, the ultimate goal of the repository is to provide access to the research community and enable analyses of the complex systems biology data, which will drive the more systematic and data driven selection of IO combination therapies. This will allow for more efficient drug trials to be conducted by companies and hopefully eliminate duplicative efforts across the field.

Approximate Project Budget

The estimated budget for this Project is based on the NCI Cancer Genomics Cloud Pilot costs and assumes we will be building upon existing resources.

(b) (4)

(b) (4)

1. \$10 million—Acquire storage and compute resources for database platform. Analysis needs to be performed to determine if in-house or cloud-based infrastructure is most appropriate. Security, Authentication, and Authorization components will be developed. Ongoing operations, maintenance, licensing, and leasing costs are included.
2. \$4 million—Develop a database platform, or “data commons,” that includes both published and unpublished data to enable data sharing. PACT will identify the appropriate data model, leveraging existing resources (e.g., NCI Thesaurus) wherever possible and work with community experts to define appropriate data models where standards do not already exist.
3. \$2 million—Identify or enhance data collection tools for the types of biomarker data prioritized to be collected from the basic and exploratory biomarkers defined in Project 1.1, while concurrently developing new tools and data collection standards for certain platforms. This will require establishment of data standards where they do not currently exist and will dovetail with Item 2 above.
4. \$2 million—Develop software/mechanisms to support data submission by participating institutions and integration, validation, and QA of that data in the CIDC.
5. \$2 million—Identify or develop tools to access and analyze the data and mechanisms to enable clinicians and basic and translational researchers to understand the promise and challenges of specific drug combinations and how to optimize treatment for patients. The PACT team understands that this amount will likely not be enough to fully develop all the tools necessary for these endeavors; however, the \$2 million will kick-start the development/enhancement of tools, which could also additionally be funded by grant programs such as Informatics Technology for Cancer Research (ITCR), as well as by private interests. In addition, it is recognized that having a critical mass of data available will be a catalyst for the community to start using it and improving upon existing tools.

This would supplement the \$1 million/year in the CIDC RFA for a total of \$30 million/5 years for both public and private sector funding.

Project 1.4—Assay standardization and validation for high priority basic biomarkers

Challenge/Opportunity

Biomarkers to improve the efficacy of immunotherapy for cancer patients are important tools in clinical management and drug development. Comprehensive profiling of the tumor immune interface with multiparametric technologies that encompass the dimensionality and complexity of the interaction of the tumor and the immune system is needed to monitor and stratify cancer patients for individual therapeutic requirements. A number of candidate biomarkers and platforms with the potential to be developed into assays to predict response to immunotherapy or monitoring have been identified in Project 1.1. The analyses are typically accomplished

through various laboratory assays to measure differences in specific tumor and immune parameters before, during, and after treatment. This may allow the identification of tumor and immune signatures, which correlate with immunotherapy response or resistance or immune related adverse events, and select patients for treatments using the biomarkers, including those identified in Project 1.1.

The diversity of reagents and approaches used in current IO research has produced a large variety of methodologies that are being used to assess the immune systems of humans and data reporting procedures that are frequently not consistent. This situation often hampers data reproducibility among laboratories, which hampers meaningful interpretation of results across studies and could lead to selection of different intent to treat populations. In addition, most of the assays used involve high-throughput multi-parametric “signatures” that require considerable statistical and bioinformatic efforts for proper algorithm development and robust data interpretation. Such capabilities are not currently available to all investigators assaying immune biomarkers and, therefore, biomarker testing is not consistently or uniformly being performed in academic or clinical laboratories due to resource constraints. Furthermore, there is no existing system that can easily integrate analyses across different clinical trials. Given these challenges, which others in the IO field have further detailed (van der Burg et al., 2011), assay standardization will be a critical focus of the PACT effort.

Different approaches to overcome these limitations and to address different technical and logistical challenges have evolved in the process of standardizing biomarkers. The importance of using standard guidelines for both specimen acquisition and analytical methods for biomarker measurements is widely recognized. First, biomarker measurements in clinical trial specimens should use high-quality, fully specified and validated assays. Second, the assay results should be comparable among clinical sites within a trial and between different trials. These goals may be achieved through use of central labs, assay standardization, harmonization, or concordance testing:

- ▶ The creation of validated assays with the kind of consistent pre-analytical, analytical, and post-analytical processes required for inclusion into clinical trials can be achieved through the **use of central laboratories** and a centralized biospecimen repository. A central laboratory that is affiliated with the entity sponsoring the trial offers the potential advantages of using the same validated assay to screen all patients and ensuring responsiveness and familiarity with the clinical trial. In addition, flexible, close communication between clinical and research teams during assay validation can be important elements for success in making a biomarker assay viable for use across different studies. Centralized testing provides assurance about the performance of a test, and minimizes differences in test performance or result reporting that can confound the definition of the intent-to-treat population within and across clinical trials. The ability to offer testing at central laboratories allows for integrated testing, sample management, and data-management services, which can facilitate efficient and reliable biomarker testing and data delivery as part of the comprehensive biomarker characterization.

- ▶ An alternative approach that facilitates the comparability and integration of data across multiple laboratories is **assay standardization**. Assay standardization and traceability to reference materials insure the most accurate and meaningful test results. Standardization also makes interpreting laboratory results easier for the physicians providing patient care. Because each assay can have its own reference interval, physicians currently must be able to apply the same reference interval to each test performed by a specific laboratory in order to accurately interpret that laboratory's results and to be able to compare across laboratories. With standardization, analytical results are more likely to be similar across all testing methods so that only one reference interval is needed, significantly decreasing the burden currently placed on physicians in interpreting laboratory results. Standardization is not a one-size-fits-all proposition. It requires development of standard unit measurement definitions, consistent calibration points, and standardized primary and secondary reference methods and/or materials for each analyte.
- ▶ Since reference materials and standards do not exist for many protein and nucleic acid analytes, **harmonization of biomarker assays** is another approach. Harmonization allows for the establishment of assay-specific protocols in individual laboratories while minimizing differences in assay performance due to assay-related variables. The use of identical reagents, instrument platforms and/or protocols and scoring criteria across laboratories is one solution, but this may not be feasible across many different laboratories. The harmonization process involves the participation of multiple laboratories in a consortium-based iterative testing process to identify the variables crucial for assay performance. To begin, individual laboratories participate to perform parallel quality control experiments on replicate samples with assay proficiency panels using the labs' own reagents, instrumentation, and protocols. A central laboratory manages logistics for the proficiency panel, receives raw and analyzed data sets from each participating laboratory, and provides independent central data analysis. During initial proficiency panels, variables are identified that impact test performance across the labs. Subsequent independent panels are then used to optimize protocols and harmonize the assay-related variables across laboratories (van der Burg et al., 2011).
- ▶ An example of an effort that addressed **concordance testing** or a comparability approach across multiple IHC-based PD-L1 tests was the Blueprint PD-L1 IHC Assay Comparison Project, which is a collaboration between the International Association for the Study of Lung Cancer, American Association of Cancer Researchers (AACR), four pharmaceutical companies (Bristol-Myers Squibb, Merck & Co. Inc., AstraZeneca PLC, and Genentech/Roche), and two diagnostic companies (Dako/Agilent and Ventana/Roche). Further detail and other examples of harmonization projects are in **Appendix 2**.

Solution

A part of methodological improvements for tumor and immunoprofiling assays provided in PACT will involve the creation of validation guidelines for immunoassays to support immune biomarker application and development for clinical trials. Part this project will enable the standardization and validation of assays to interrogate the IO biomarkers identified in Project 1.3. Standardization

and validation of the assays to be used for multisite trials and across different trials should minimize variability in assay results and provide an opportunity for comparability across sites and studies. Achieving a high level of data reproducibility and data comparability will help to accelerate the development of therapeutics targeted to specific biomarker-selected patient populations.

Focus of the Project

This project will likely have two aspects: 1) assay standardization/harmonization and 2) establishment and distribution of standard operating procedures (SOPs) and best practices.

1. Assay standardization/harmonization

First, 1–2 core laboratories from within the core laboratory network will be selected to validate existing assays for the PACT basic biomarkers. These laboratories should be able to establish technically and analytically validated assays that include several continuous steps of biomarker development. Technical and analytical validation refers strictly to the performance of the assay. Assay clinical validation occurs as part of the outcome analysis in clinical trials that ensures that the assay performs robustly according to predefined specifications (fit-for-purpose) that will establish acceptable criteria for use in future studies. Clinical utility, which refers to establishing the use of a biomarker test leads to a favorable benefit-to-risk balance, that is, guides clinical decisions that lead to better outcome, should also be planned.

PACT projects can be tasked to address various aspects of assay validation and standardization for selected markers based on the PACT JSC recommendation:

- ▶ **Evaluation of pre-analytic factors:** An important step in biomarker validation is the evaluation of **pre-analytical factors** that may affect assay performance due to specimen-related variability. For immunotherapies, for example, there may be a need to monitor *ex vivo* immune responses in phenotypical or functional assays, which require high-quality samples to ensure reliable analytic output. To ensure that optimal pre-analytic processing regimens are followed, SOPs for controlling specific biomarker development steps are essential. In general, best practice metrics can be defined for various parameters depending on the specimen type to be used. For instance, protocols for blood collection and processing, tumor collection, sample fixation and processing, and storage media optimization are often developed. To improve standardization of specimens, NCI has published best practice guidelines for biospecimen collections (National Cancer Institute, 2011). PACT will endeavor to follow these published guidelines where possible and make modifications where needed. Additionally, pre-analytical considerations for certain assay types can be found in **Appendix 2**.
- ▶ **Technical and analytical validation:** Analytical validation involves establishing the performance of an assay for its intended biomarker measurement. Analytical validation studies can include 1) accuracy, 2) precision, 3) analytical sensitivity,(4) analytical specificity, 5) reportable range of test results for the test system, 6) reference intervals (normal values) with controls and calibrators, 7) intersite reproducibility if the assay is to be performed in multiple laboratories, and 8) establishment of appropriate quality control measures (Becker,

2015; Jennings, Van Deerlin, Gulley, & College of American Pathologists Molecular Pathology Resource Committee, 2009; Landis & Koch, 1977; Linnet & Boyd, 2012; Mandrekar & Sargent, 2009). There are also validation study considerations depending on the type of assay and specimens that are used. For example, reader precision studies are needed for IHC tests, whereas molecular assays require accuracy studies. Whether the assays are for integral, integrated, or exploratory biomarkers, they must be fit-for-purpose and meet the acceptable criteria defined for the intended use in patients and trials. PACT will be able to use samples from trials that participate to perform technical validation of assays, when deemed necessary and approved by the trial sponsored.

- ▶ **Clinical validation:** After an assay has been analytically validated, PACT-associated laboratories may also be able to carry out **clinical validation** of the assays to determine whether the assay result has a clinically meaningful correlation with the condition of interest—for example, whether the assay reliably divides the patient population(s) of interest into distinct groups with divergent expected outcomes to a specific treatment. The laboratories will be asked to perform assays for integral biomarkers (for treatment eligibility) in a CLIA-compliant laboratory, and use of the test in a trial may need to be performed under an IDE from the FDA if it is a significant risk trial. This aspect will not be a requirement of all PACT-associated laboratories.
- ▶ **Assay harmonization and concordance testing:** For certain biomarkers and assay platforms, there may be a need for assay harmonization between labs or testing of concordance between validated assays. Such projects will be prioritized by the PACT Joint Steering Committee depending on the scientific importance or the clinical trial needs of PACT to have these assays become part of the basic biomarker modules and uniformly performed across all PACT-associated trials.

2. Establishment and distribution of SOPs and best practices.

The PACT core laboratory network group will create a **committee** to coordinate efforts and to promote synergistic research efforts among the core laboratories. This Core Laboratory Committee (CLC) will meet monthly and review progress in developing biomarker assays and report its findings to the PACT JSC. It would operate as a work group of the JSC, but would remain a separate entity reporting to the NCI CIMAcs. The CLC will select best practices from the CIMAcs and generate and distribute SOPs and other materials among the core laboratories to keep the assays standardized and updated with best practices. These SOPs and materials will be shared with external partners that wish to run the PACT modules in their trials and contribute their data, but not use the PACT core laboratory network.

Evaluation and prioritization of biomarkers and platforms for which validation will be required will be assessed by the PACT JSC.

Value Proposition

The biological complexity of the tumor and immune system interaction poses multiple challenges associated with technical development of clinically applicable assays when evaluating different variables as markers of clinical benefit to immunotherapy. However, each of the potential biomarkers and their associated assays requires high-quality validation in order to be used effectively in clinical applications. Considering the increased relevance and emphasis on biomarker development in cancer immunotherapy, there is an enormous need to facilitate and improve the steps to demonstrate clinical value of molecular diagnostics in this space. PACT will apply standardized approaches for biomarker validation described above, when necessary, to enable more efficient assay development to identify IO-relevant biomarkers, which are crucial to guide personalized therapy and for advancing IO options for cancer patients.

Approximate Project Budget

The cost of this project will be tied to the time and resources necessary to establish an analytical performance of each assay. Because flow cytometry, IHC, DNA/RNA sequencing, and other analytical methods constitute a large segment of the molecular characterization of the tumor and immune profiling, they will likely be the first validated for specific use. The estimated cost for running each assay for validation is \$500–\$1,000/sample, depending on the assay type (~\$500/sample for IHC versus ~\$1,000 for some flow cytometry panels), with the likely need to perform comprehensive analysis of 100 samples to validate any assay head-to-head. Cost for one assay comparison would then be ~\$50,000–\$100,000. For more complex assays, there could be additional costs even beyond this estimation. There would also be additional costs associated with time of the technical staff, biostatistical staff, and computer scientists for stand-up of the assays within the labs and the postanalytical phase of assay validation. The hope is that these costs could be partially defrayed since the CIMACs will already be established. In addition, PACT would hope that the cost for the samples for these validation assays would also be low due to the availability of banked samples in the PACT biorepository.

Project management and organizational support for the panel and team will also be required in order to assemble and keep current the materials for the drafting and review of the SOPs. A small team to do this—contracted separately from the core laboratory network and including one project manager and one science writer at full-time salary and benefits, plus the meetings and supplies—would cost ~\$400,000/year.

The following table summarizes the total budget for Program Area 1:

Program Area 1 Consolidated Budget

PROJECT PLAN SECTION	BUDGET ITEM/ PROJECT GOAL	NIH/NCI CONTRIBUTION	PRIVATE SECTOR CONTRIBUTION			TOTAL PROJECT COST (b) (4)
			DIRECTS	INDIRECTS	TOTAL	
Project 1.1.1 and 1.2	Create core laboratory network to conduct biomarker assays					(b) (4)
Project 1.1.2	Develop new IO biomarkers					
Project 1.1 and 1.4	Expand biorepository capabilities for sample storage					
Project 1.3	Create database to bank IO biomarker data from clinical trial					
Project 1.4	Standardize and harmonize biomarker assays for IO therapy					
PROGRAM AREA 1						\$205.75M
Program Area 1 — “Buy-up” Option ► Supplement to defray costs of additional tissue collection at clinical sites						

Program Area 2: Provide scientific coordination for the selection of clinical combination therapy trials important to the field but not already being performed elsewhere, and co-fund such trials with partners

Project 2.1 – Landscape analysis and literature review of biomarkers being developed and IO and other therapy combinations being tested across the oncology field

Challenge/Opportunity

One of the primary hurdles the PACT initiative will face is that the field of IO is moving at such a rapid pace compared even with other portions of the cancer research and clinical fields. This accelerated pace of research, drug development, drug release, and clinical use of IO therapies will make it challenging for PACT to select which biomarkers to develop and test unless these deliberations are accompanied by a “real time” effort to gather information on all of the current trials and related activities in the field. Specifically, the Scientific Project Selection Panel (SP²) and Joint Steering Committee (JSC) will need guidance on which biomarkers and combination therapies are being tested or are in development. A crucial piece to development of this guidance will be to produce it quickly as the timeline will need to parallel the IO drug development pace.

Solution

To stay current and synergize most effectively with other efforts in the IO and oncology field, we propose to have a small team of science researchers and writers regularly conduct a landscape analysis of critical efforts in the IO field. The first fully comprehensive landscape analysis will occur just after the launch of the PACT initiative. This comprehensive analysis will likely take approximately 1–3 months to fully research all publically available information about ongoing biomarker and combination trials within the IO space that have taken place to date, and then compile that data into a digestible format for the SP² for review. This group will also engage with PACT company members to acquire data on the emerging company trials, as well as to gain any organizational insight into the IO landscape that can assist in the selection of combination therapies and biomarkers to be addressed through PACT.

The landscape analyses will include publically available data from publications, websites (e.g., clinicaltrials.gov and others), abstracts, and corporate websites and publications, as well as insights gleaned directly from conversations with relevant industry representatives, both PACT and non-PACT members as appropriate. Both public and private information will be collected, and the FNIH (or its contractor) will act as a neutral third party to collect the data. Two versions of a summarized report will be generated: 1) a high-level summary devoid of any proprietary data, which can be reviewed by the entire PACT JSC to assist in decisions, and 2) a more detailed summary which may include some proprietary data—as necessary and if willing to be shared--to be reviewed only by the SP² (which, it should be recalled, will include no members of competing pharmaceutical companies, but only academics and ex-company members with no conflicts of interest). The authors of the landscape analysis as well as the SP² members will be bound by confidentiality agreements.

From this analysis, the team will create and maintain an up-to-date summary clinical trial compendium for combination therapies and biomarkers in development from current and emerging data across the entire IO space enabling categorization of trials into three types: 1) highly relevant to the entire IO field, funded trials; 2) proposed trials that are highly relevant to the IO field but currently unfunded; and 3) trials of low relevance. The SP² will review this compendium and use it to make recommendations to the JSC about which trials and resulting biomarker modules PACT should pursue, and which trials PACT should help to co-fund. As a secondary feature, the SP² will also be able to make recommendations to the IO outreach team about which groups to work with to develop cross-fertilization efforts and which other groups to approach about depositing their trial data into the PACT database for harmonization with PACT biomarker modules.

After this initial landscape analysis is generated, it will be shared with the appropriate governing bodies for PACT to allow them to make their initial decisions. A landscape update will be conducted biannually each year the PACT initiative continues. These biannual updates will take place in the month immediately following the annual meeting for the American Society of Clinical Oncology (ASCO) and the European Society for Molecular Oncology, which usually occur in early summer and late fall. These meetings usually have the largest release of data from all stakeholder groups relevant to the PACT initiative and therefore will be ideal targets for the landscape updates. While these meetings will be the primary target for data review due to the large amounts of new data released, the analysis will also be sure to account for data released at other meetings in the time between landscape scans, such as the ASCO, American Society of Hematology, American Association of Cancer Research annual meeting, and others. After each update, a report similar to that generated after the initial landscape analysis will be prepared and shared with appropriate committees.

Value Proposition

A full picture of current and upcoming biomarker testing will allow the PACT teams to continuously update its pipeline of basic and exploratory biomarker modules. Having the most current list of IO combinations being tested will also allow the PACT initiative to approach

the right individuals with whom to discuss incorporating their markers and trials into PACT, and help construct a knowledge base to help guide the field with respect to choosing future combination studies.

The landscape analysis will also help support the active outreach to other groups that are working in the IO space described as part of Project 2.2.

Approximate Project Budget

(b) (4)



The total cost for this project is therefore estimated at ~\$1 million dollars over the 5 years.

Project 2.2 – Selection of trials with high-priority combination therapies and biomarkers for co-funding by PACT

Challenge/Opportunity

As mentioned above, PACT will not establish its own clinical trials network infrastructure or fully sponsor and conduct the trials itself (i.e., contract with selected clinical sites; finance and monitor patient accruals; hold INDs; conduct safety reporting; submit registrations etc.), but will work with existing trial networks to implement clinical trials that will use the PACT biomarker modules. These clinical trials may come from the NCI's clinical trial networks (e.g., ETCTN, NCTN, CITN, and COG), industry, academic investigator-initiated trials, or nonprofit consortia (e.g., Stand Up 2 Cancer, Parker Foundation IO Consortium), provided groups are willing to work with PACT and implement the biomarker modules within them. Partner trials will be selected by the PACT JSC based on the landscape analysis described in Project 2.1 after review by and based on the recommendations of the SP². JSC will next work with an outreach project team from FNIH to help broker a partnership for PACT biomarkers on those trials and eventual deposition of the data into the common database. This outreach project team could also encourage companies or other trial networks to initiate new trials using some of the high-priority combinations identified by the SP² if these trials are not currently in the pipeline. (This is further described in the description of Project 2.3 below.) The PACT team also recognizes there will be a few particularly high-value combination trials to be conducted that need some supplemental funding in order to be launched, as they may not be within the short-term pipeline of any company. PACT will work

to facilitate partnerships between the necessary companies to initiate these trials, PACT can consider providing supplementary funding to conduct these trials through mechanisms already available, or it may choose to institute a unique RFA mechanism for these trials.

The following are some examples of how this will work:

- ▶ **Example 1: PACT initiates new trials for novel combinations and supports the relevant biomarker studies:** A new high-priority treatment or combination regimen is identified by the SP², and the JSC decides it should be a PACT trial because the biomarker and clinical objectives would fill critical gaps in the field. However, the companies with the compounds of interest are not able to prioritize their resources to fund the clinical and biomarker studies in their entirety. (Or, alternatively, PACT proposes new trials for combinations already in clinical testing, but finds that additional studies with alternate designs or clinical settings are needed (e.g. with pharmacodynamic endpoints or biomarker stratifications) to address critical biomarker or clinical questions not otherwise tested.) In this case, PACT approaches the companies and offers to help support the costs of the biomarker testing. The size of the trials may range from small phase I/pilot studies to larger phase II trials. As an example, one could estimate a trial of 50 patients to cost ~\$6 million. PACT could invest ~\$2 million to conduct the biomarker assays and some site supplements. If the trial were to be conducted through the CTEP infrastructure, CTEP would supplement payments to trial sites to cover ~\$2 million. This would then leave the companies with only ~\$2 million to raise to conduct the trial. It is the hope that this reduced cost would incentivize the companies to participate in the trial as part of PACT.
- ▶ **Example 2: PACT supports biomarker studies in ongoing/planned trials:** The SP² identifies an existing clinical trial involving immunotherapies that are suitable for high-priority biomarker studies, and the JSC decides it would fit well as a PACT trial. However, the companies sponsoring the trial are only able to conduct limited biomarker assays. In this case, the PACT team will approach the sponsoring companies (or clinical trial network, depending on the trial structure) and ask them to collect samples to run at least the basic biomarker modules in their trial. In this case, PACT pays for the testing of these biomarkers only. If one assumes this is a phase I/II trial with a cohort of 50 patients, then the PACT supplement for this trial would consist of \$500,000 to conduct the biomarkers plus an additional \$500,000 to supplement collection and storage of the additional samples needed for the biomarker testing. This would result in a total of an approximately \$1 million trial supplement. Trials of this type could come from either the NCI Clinical Trials Networks or from the private sector.
- ▶ **Example 3: PACT supports biomarker studies in completed trials:** The SP² identifies a clinical trial of a high-priority therapy combination or biomarker objectives that has already been conducted and for which properly banked biospecimens are available, and the JSC decides it would fit well as a PACT trial. PACT funds the conduct of basic biomarker modules on the samples. (This may be phase I, II, or III trials.) The cost to run the basic biomarker modules would be tied to the number of patient samples. If the trial collected 200 patient samples, the cost would be ~\$2 million to run the basic biomarker assays.

As noted in each of the examples, once drug combinations of interest or existing clinical trials are identified and the decision to provide PACT support has been made, the PACT outreach team from Project 2.3 will work to recruit the necessary partners. In addition, as the PACT program develops, a mechanism can be established for teams to send proposals for priority combination therapy trials to the JSC for review independent of the landscape analysis.

Value Proposition

Co-funding trials through PACT will enable trials that would not normally be conducted by companies on their own, but that have high potential value to the field, to be conducted, with the resulting data shared with the research community. Co-funding could also be a means to conduct retrospective biomarker assays on banked samples from high-priority data that would substantially add to our understanding of the science behind IO and related combinations.

Approximate Project Budget

Costs for this project will be partially accounted for in the biomarker budget for Project 1.1, as one of the main aspects of co-funding will be to pay for testing of the biomarkers for the trials. However, it is anticipated that there will also be a need for funding for an RFA to support 5–10 of the highest-priority trials to be conducted during the first 5 years of PACT. It may also be possible to create an RFA for clinical trials through either the ETCTN or NCTN. (b) (4)

Co-funding could range from simple biomarker support to partial trial funding. The RFA could be administered either through FNIH or NCI depending on the desired needs and structure of the partnership.

Further PACT Trial Co-Funding (Optional)

The amount for co-funding detailed here represents an initial investment by PACT to assist in getting important trials conducted. (b) (4)

This further funding can be determined in future years and on a trial-by-trial basis with the funding partners if the PACT model proves to be successful.

Project 2.3 – Active outreach and coordination with other ongoing IO/oncology efforts

Challenge/Opportunity

As a logical counterpart of its biomarker development, assay standardization, data integration, and trial (co-)funding mission, PACT is designed to serve as a clearinghouse and coordination point for information and insights on potential IO and combination therapy research. Given this PACT will need to coordinate actively with the many existing and emerging public and private research efforts in the field.

Solution

A scientific program management team at FNIH and experienced in facilitating the work of public-private partnerships will leverage the information from the landscape analyses that are ongoing in Project 2.1 to conduct targeted outreach and establish external collaborations with similar programs supported by biopharmaceutical companies, nonprofits, academic medical institutions and government agencies. This team will work to coordinate efforts continuously across all active IO efforts, avoid duplication, share information, and ultimately meet the PACT objective of a systematic translation, evaluation and validation of biomarkers and assays.

Value Proposition

A proactive, constant outreach to and involvement of other IO/combination efforts will allow the most efficient use of the investments of PACT stakeholders and there sources available in the field, given biological complexity of immunotherapies and related combinations and the breadth and depth of what must be learned in order to deliver effective treatments to patients.

Approximate Project Budget

(b) (4)

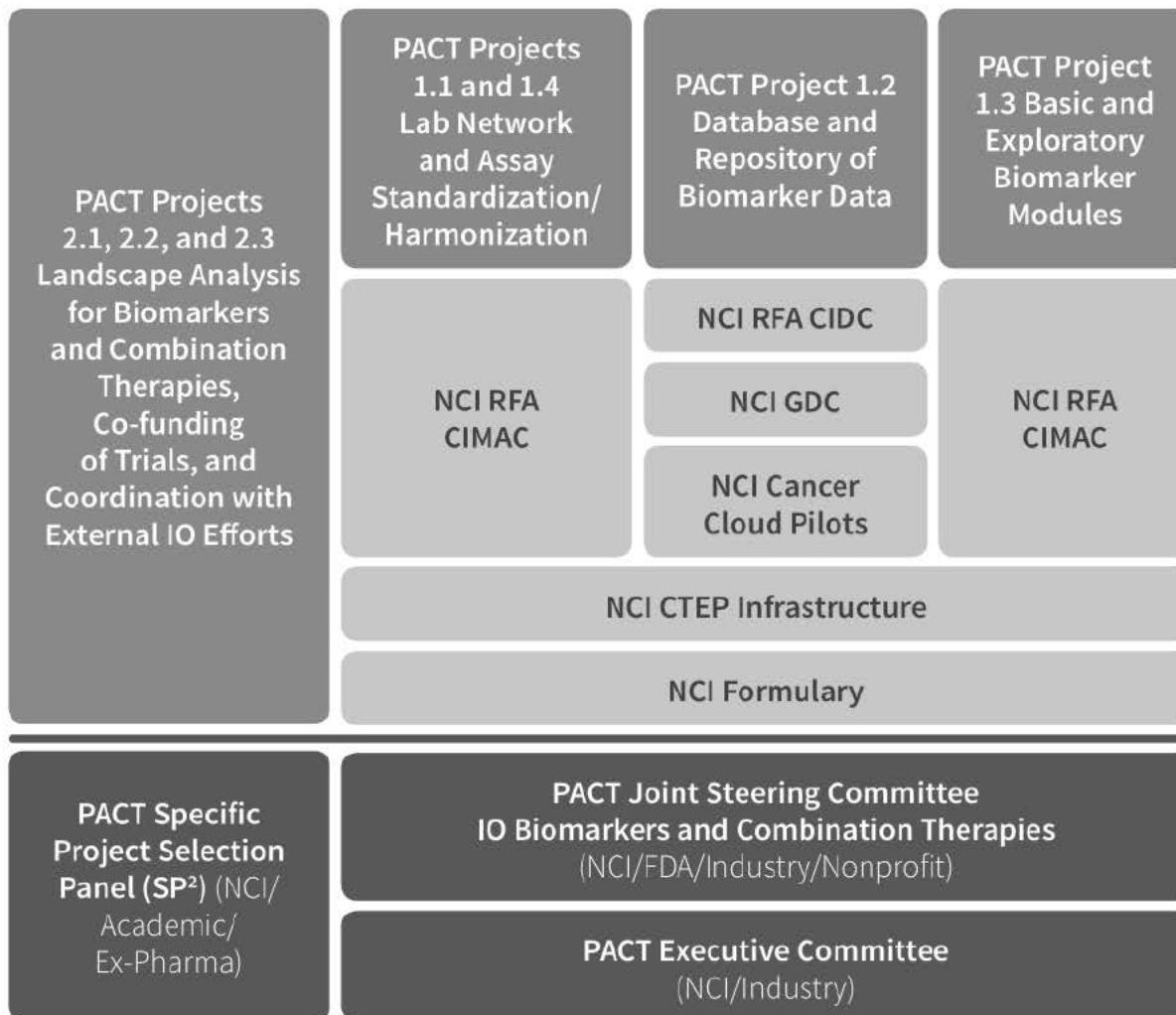
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The following summarizes the total costs to support Program Area 2:

Program Area 2 Consolidated Budget

PROJECT PLAN SECTION	BUDGET ITEM/ PROJECT GOAL	NIH/NCI CONTRIBUTION	PRIVATE SECTOR CONTRIBUTION			TOTAL PROJECT COST
			DIRECTS	INDIRECTS	TOTAL	
Project 2.1	Conduct biannual landscape analysis to determine priority biomarkers and combination therapies					(b) (4)
	Compensate SP ² members for trial and biomarker landscape review					(b) (4)
Project 2.2	Co-fund high-priority combination clinical trials					
Project 2.3	Conduct outreach and coordinate with other IO efforts					
PROGRAM AREA 2						\$28.65M
Further PACT Trial Co-Funding (Optional) ► Additional funding for specific clinical trials and biomarkers, which can be decided on a trial-by-trial basis						

PACT Governance



- [FNIH Managed Private Sector Raised Funds] FNIH Managed Private Sector Raised Funds
- [NIH Managed Funds] NIH Managed Funds
- [Governance Bodies] Governance Bodies

To achieve its objectives, PACT will require a governance structure that 1) maintains close involvement by both public and private partners in key decisions; 2) protects confidential or proprietary information and guards against conflicts of interest; 3) provides both continuous strategic direction for the partnership and rigorous operational management of its different component parts; and 4) enables timely decision-making, avoiding unnecessary bureaucracy. To accomplish these goals, we propose four **focused governing bodies to run the partnership**:

1. An operationally focused PACT Joint Steering Committee (JSC), each member of which will direct different aspects of the PACT research plan.

2. A PACT Scientific Project Selection Panel (SP²) to analyze existing and potential therapeutic and biomarker studies and make recommendations regarding which biomarker studies could be executed as part of PACT. This will be an advisory rather than decision-making body. The JSC will make the actual selection of which trials should be part of PACT based on the SP²'s recommendations.
3. A PACT Executive Committee (EC) to provide high-level strategic direction, communication with the top leadership of each of the partner organizations, and resolution of general policy issues. The EC will oversee the actions of the JSC and the SP² and communicate with other PACT partners via an Extended Executive Group, consisting of senior executives from partner organizations not actively serving on the EC.
4. In addition, a PACT Patient Advisory Committee (PAC) will be added to the governance structure of PACT upon the launch of PACT years 4-5, consisting of representatives from cancer patient advocacy organizations. The PAC will periodically review the progress of PACT and provide input to the EC and JSC on PACT's relevance to and support of cancer patient needs and concerns.

PACT Joint Steering Committee (JSC)

Execution of the research programs in PACT will be governed through a JSC composed of members from participating companies, government agencies, and nonprofit organizations. The JSC will operate under the direction of the PACT Executive Committee (EC).

The responsibilities of the JSC will include:

1. Reviewing the recommendations of the PACT SP² (described below) and using these recommendations to set operational research priorities for PACT programs, including selecting the optimal combination therapy trials for PACT partnerships.
2. Reviewing the progress of projects on an ongoing basis and adjusting project plans to ensure appropriate tradeoffs between the timely achievement of key project milestones and production of quality results. The JSC is therefore the primary forum for discussion among the PACT partners of potential operational changes to the final research plan, based on emerging opportunities and challenges, and within the context of the project budgets.
3. Meeting regularly with the Core Laboratory Committee (CLC) to ensure lab coordination and development and distribution of SOPs and best practices.
4. Conducting assessments of key project milestones, including critical go/no-go milestones, and communicating these assessments to the EC.
5. Determining how private sector funds provided to FNIH are distributed (consistent with the final research plan).
6. Working with the potential PACT PAC, which will be composed of patient advocates.

7. Reviewing the results of the research efforts under PACT and making recommendations regarding how they are disseminated and publicized, consistent with NIH publication rules.
8. Overseeing active outreach to, and coordination with, other related cancer research and trial efforts as described in Project 2.3 (above).

While the final overall research plan for PACT will be decided jointly by NIH/NCI and industry partners, the funds provided by NIH and industry for PACT will flow through separate streams. NIH funds must be disbursed according to NIH procedures for solicitation of applications, review of applications, and decision-making. NIH will have final statutory decision-making authority over the conduct of its grants, as provided in the federal regulations, although private sector partners will have the ability to provide input on the progress of the NIH-funded research through the JSC.

Private sector partner funds will be contributed through and managed by FNIH. (FNIH will also coordinate any material in-kind private sector contributions to PACT.) Such funds may be dispersed directly by FNIH through grants or contracts, or transferred by FNIH to NIH for disbursement through NIH grants. The JSC will review and select proposals made directly to FNIH for funding. After awards are made, the JSC will provide project oversight for all studies, whether funded by NIH or industry/FNIH, in a manner consistent with NIH procedures as described above.

The membership of each of the JSC will be as follows:

- ▶ Three to four NIH members (voting), including program officials for the relevant NIH grants
- ▶ At least one representative from FDA (nonvoting)
- ▶ One voting representative from each funding industry partner; additional industry representatives may attend as alternates but will be nonvoting
- ▶ One voting representative from each nonprofit organization that matches company funding levels for PACT
- ▶ Subject matter experts, such as academic investigators, whether funded by PACT or not; may be added at the JSC's discretion, but will be nonvoting
- ▶ At least one representative from FNIH (ex-officio, nonvoting)

The JSC will be co-chaired by one NIH and one industry representative, selected by the PACT EC, but who is not part of the EC.

After the projects are launched, the JSC will meet regularly (likely monthly) via teleconference, and at least twice yearly in person. The frequency of meetings will be adjusted as the scientific agenda requires. The JSC may also convene smaller “working groups” of experts that include PACT stakeholders to advise on specific areas of science or technical aspects of the research plan. The decisions of the JSC will be made by simple majority. Each participating company will have one vote as will each qualifying nonprofit partner, and the resulting private sector cumulative

vote will remain constant at 50 percent of the total votes. If additional industry members are added to the partnership, votes for all industry participants will be scaled appropriately. NIH will have votes that will not exceed 50 percent of the total. The goal of the JSC will be to drive consensus on partnership decisions. In the unlikely event that this cannot be achieved, any conflicts will be raised to the EC for resolution. JSC operational logistics, staffing, and project management will be managed by FNIH.

PACT Scientific Project Selection Panel (SP²)

Some of the most important decisions made in the course of PACT involve choosing appropriate studies or projects to execute using the PACT infrastructure or with PACT funding. These include consideration of which biomarkers or preclinical models to develop, around which drugs or drug combinations these efforts should be focused, and—for Program Area 1 (biomarkers)—which clinical trials should be selected to have biomarker studies executed in PACT (Program Area 2). We expect that proposals to execute combination clinical trials with biomarker studies defined in the modules within PACT will be of several different types:

1. A proposal for a biomarker “companion study” to be run using an NCI-sponsored (ETCTN or NCTN) trial as a “backbone,” where samples and clinical data collected from such trials are run through the PACT infrastructure.
2. A proposal to test combinations brought to PACT by one or more industry partners, where samples and data collected from these trials would be developed using the PACT core labs.
3. External sponsors of individual trials could also choose to run PACT biomarker modules using PACT-developed assays and standard SOPs in labs they select outside the PACT core labs and contribute data back to the NCI Data Commons.

Evaluating studies that are proposed to run under PACT or which datasets to accept into PACT will require significant scientific expertise, potential access to sensitive or confidential company data (such as proposed trial protocols, results of point of care or early-phase preclinical or clinical studies, investigator brochures), and the ability to provide objective recommendations that are based on the science rather than individual commercial considerations. In this regard, the JSC will need to rely on advice from a separate panel of oncology experts who are knowledgeable about oncology (with a particular focus on IO) and who have practical experience in biomarker and therapeutic development, but can provide objective advice and are free of conflicts of interest with regard to the interests of specific companies. PACT will establish the SP² to fill this advisory role.

The SP² will determine which potential therapeutic combinations and which biomarkers have the highest priority for assessment in the PACT infrastructure. The SP² will oversee the conduct and distribution of the landscape analysis described in Project 2.1 above and will use information from the landscape analysis and other sources to identify candidate studies for PACT. FNIH will provide research services (through a subcontracted consulting group if needed) to collect

the background information needed to assess these studies. FNIH (or its subcontractor) will execute the necessary confidentiality agreements with companies and other entities whose studies are being considered by the SP² and with individual SP² members to ensure proprietary or confidential information is used only to support PACT decisions and is protected from inappropriate disclosure. The SP² will focus on combinations that address currently unmet needs for the field and for patients (i.e., are not effectively being tested elsewhere) and that offer a compelling scientific rationale for inclusion in PACT and make specific recommendations to the JSC about which studies to pursue. The SP² may also communicate its most general findings more broadly where they may be of use to specific sponsors or to the oncology community.

The membership of the SP² should include the following:

- ▶ NCI scientists and medical officers with expertise in PACT interest areas. This may include one or more members of the JSC who can act as liaisons.
- ▶ FDA scientists.
- ▶ Academic researchers with relevant clinical and translational research expertise. These members, while they serve on the panel, will not be able to serve as principal investigators on studies associated with PACT.
- ▶ Scientists with industry experience in oncology drug development who do not have current employment with or active ties to individual companies in the areas of interest for PACT, to avoid conflicts of interest.
- ▶ One or more representatives from nonprofit/patient organizations with an interest in IO.

The SP² will meet at least quarterly (or more often if needed) by teleconference. Two of these quarterly meetings will be set to correspond to the completion of the twice yearly landscape analysis updates. The SP² will be co-chaired by one NIH and one academic researcher and will report to the PACT EC. Each member will have one vote; decisions will be made by simple majority. In the unlikely event that consensus cannot be achieved, conflicts will be raised to the EC for resolution. SP² operational logistics, staffing, and project management will be managed by FNIH.

PACT Executive Committee (EC)

The PACT EC will be responsible for oversight of PACT, ensuring that the partnership overall is conducted efficiently and in the best interests of patients and the public health, and for communicating the value of PACT to its partners and the public. Specifically, the EC will be responsible for the following:

1. Providing general guidance for the overall strategy of PACT within the rapidly changing oncology landscape.

2. Reviewing the progress of PACT on a regular basis and ensuring its effective and timely execution. This includes review and approval of major go/no-go milestones and funding changes.
3. Communicating the progress of PACT and any related challenges to the partners and the oncology community, and managing the relationships among the partners.
4. Establishing the policies that govern PACT and ensuring they are adhered to.
5. Overseeing the operation of the PACT JSC and SP², and resolving any conflicts or questions that they may not be able to resolve on their own.
6. Considering new initiatives or partners that may be added to PACT over time.

The membership of PACT (voting, except where otherwise noted) will include the following:

- ▶ The Director of the National Cancer Institute (or the Director of the Division of Cancer Treatment and Diagnosis) at NCI's discretion
- ▶ The Deputy Director of NCI
- ▶ The Director of CTEP, Division of Cancer Treatment and Diagnosis, NCI
- ▶ Two representatives from FDA (representing both CDER and CDRH)
- ▶ A patient advocate representative
- ▶ Three senior-level executives from three different biopharmaceutical company partners (head of research and development or global head of oncology research or development)
- ▶ A representative from the NIH Office of the Director (ex-officio, nonvoting)

The EC will be co-chaired by one senior official from NCI and one senior executive from one of the industry partners. It will meet at least quarterly by teleconference and will seek opportunities to meet periodically in person as schedules allow. Voting will be by simple majority.

To insure effective communications with and input from all PACT stakeholders, an Extended Executive Group, consisting of the EC members and representatives from the private sector partners not currently included on the EC, will be established to receive regular updates on PACT and advise the EC on its progress and direction. The Extended EC will meet twice a year by teleconference. The EC and the Extended Executive Group will be convened and supported by FNIH.

Consolidated Total Budget Estimate

The following table summarizes the budget inputs from Program Areas 1 and 2 into a single high level view of the total PACT budget:

CONSOLIDATED ITEMIZED PACT BUDGET							
ALL COSTS REFLECT TOTAL OVER 5 YEARS							
PROJECT PLAN SECTION	BUDGET ITEM/ PROJECT GOAL	NIH/NCI CONTRIBUTION	PRIVATE SECTOR CONTRIBUTION			TOTAL PROJECT COST	ASSUMPTIONS/SCOPE
			DIRECTS	INDIRECTS	TOTAL		
Project 1.1.1 and 1.2	Create core laboratory network to conduct biomarker assays		(b) (4)		\$102M		(b) (4)

CONSOLIDATED ITEMIZED PACT BUDGET							
ALL COSTS REFLECT TOTAL OVER 5 YEARS							
PROJECT PLAN SECTION	BUDGET ITEM/ PROJECT GOAL	NIH/NCI CONTRIBUTION	PRIVATE SECTOR CONTRIBUTION			TOTAL PROJECT COST	ASSUMPTIONS/SCOPE
			DIRECTS	INDIRECTS	TOTAL		
Project 1.3	Create database to bank IO biomarker data from clinical trials			(b) (4)	\$40M		(b) (4)

*Indirects lower for this project because a majority of work will occur at NCI and not academic institutions.

CONSOLIDATED ITEMIZED PACT BUDGET							
ALL COSTS REFLECT TOTAL OVER 5 YEARS							
PROJECT PLAN SECTION	BUDGET ITEM/ PROJECT GOAL	NIH/NCI CONTRIBUTION	PRIVATE SECTOR CONTRIBUTION			TOTAL PROJECT COST	ASSUMPTIONS/SCOPE
			DIRECTS	INDIRECTS	TOTAL		
Project 1.1.2	Develop new IO biomarkers					(b) (4) \$40M	(b) (4)
Project 1.4	Standardize and harmonize biomarker assays for IO therapy					\$11.25M	

CONSOLIDATED ITEMIZED PACT BUDGET							
ALL COSTS REFLECT TOTAL OVER 5 YEARS							
PROJECT PLAN SECTION	BUDGET ITEM/ PROJECT GOAL	NIH/NCI CONTRIBUTION	PRIVATE SECTOR CONTRIBUTION			TOTAL PROJECT COST	ASSUMPTIONS/SCOPE
			DIRECTS	INDIRECTS	TOTAL		
Project 1.1.2 and 1.4	Expand biorepository capabilities for sample storage		(b) (4)		\$12.5M		(b) (4)
PROGRAM AREA 1					\$205.75M		
Project 2.1	Conduct biannual landscape analysis to determine priority biomarkers and combination therapies				\$1.15M		
	Compensate SP ² members for trial and biomarker landscape review				\$0.5M		

CONSOLIDATED ITEMIZED PACT BUDGET							
ALL COSTS REFLECT TOTAL OVER 5 YEARS							
PROJECT PLAN SECTION	BUDGET ITEM/ PROJECT GOAL	NIH/NCI CONTRIBUTION	PRIVATE SECTOR CONTRIBUTION			TOTAL PROJECT COST	ASSUMPTIONS/SCOPE
			DIRECTS	INDIRECTS	TOTAL		
Project 2.2	Co-fund high-priority combination clinical trials				(b) (4)	\$27M	(b) (4)
Project 2.3	Conduct outreach and coordinate with other IO efforts						
PROGRAM AREA 2						\$28.65M	
FNIH Program Management Costs						\$16.6M	
PACT Initiative Total						\$251M	
Program Area 1—“Buy-up” Option							
Program Area 2—“Buy-up” Option							

Appendices

Appendix 1: Exploratory Biomarker Modules – Detailed Description

Evaluation of unknown biomarkers can be performed depending on availability of samples from the periphery and tissue and specific objectives of the relevant clinical trial. Various stakeholders (e.g., National Cancer Institute or company sponsor) can choose to fund these modules based on specific trial objectives or shared objectives across multiple studies.

Module 1c: Immune Cell Biology

As a potential expansion to the study of the immune cell biology to develop novel biomarkers, the PACT team suggest single-cell sequencing of tumor cells and immune cell subsets on a small number of tumors, such as myeloid-derived suppressor cells (MDSC), tumor-associated macrophages (TAM), neutrophils, T-cell clonality, and the use of newer technologies such as NanoString and CyTOF imaging, can be used to understand immune cell characterization, cell trafficking, and spatial co-localization of multiple cell types in the tumor microenvironment (TME).

Focus of the Project

Tumor and Periphery

- ▶ Analyze and compare different immune cell populations in the tumor and periphery (blood) by immunohistochemistry (IHC) and flow cytometry (or CyTOF) with standard operating procedures and quality-controlled experiments. Examples of potential markers are listed in Table A-1.

TABLE A-1: EXAMPLES OF CELL POPULATIONS

CELL POPULATIONS/MARKERS (EXAMPLES)
T cells (e.g., CD3, CD8, CD4, CD45RO, FoxP3, TIM3, LAG3, PD1, etc.)
NK cells (e.g., CD5, CD16, etc.)
B cells (CD19, activation markers, etc.)
Macrophages (e.g., CD163, CD206, CD64, etc.)
Dendritic cells (e.g., CD11c, CD1c, CDC141, HLA-DR, ILT7, etc.)
MDSCs (e.g., OLR1, CD15, CD14, etc.)
Neutrophils
Mast cells
Eosinophils

- ▶ Use similar marker set for flow cytometry and IHC, when possible:
 - ▷ Have multiple methods assessing same markers to ensure quality data.
 - ▷ Flow cytometry allows for quantification of immune cell subsets.
- ▶ IHC allows for analysis of localization of different immune populations (e.g., in T-cell- rich/poor areas, edge, etc.).
- ▶ Depending on sample size, ability to do multiple panels will allow evaluation/quantification of larger number of markers than IHC. Will need to propose prioritized panels if sample is limiting.
- ▶ Functional cell analysis (e.g., T-cell and MDSC assays).
- ▶ Compare immune cell subsets in blood versus tumor.
- ▶ New assay formats allowing visualization of the 3-dimensional immune architecture of selected larger tumor samples (perhaps from pre-operative trials/window of opportunity trials) could be explored. This would expand knowledge obtained from standard IHC (Gerner, Kastenmuller, Ifrim, Kabat, & Germain, 2012; Gerner, Torabi-Parizi, & Germain, 2015).
 - ▷ Program infrastructure (clinical and bioinformatics) should be established with a view that technology combining assessment of molecular markers in the context of tumor (maybe tumor-draining lymph node as well) spatial architecture will evolve and will need to be incorporated in the future.

Module 2b: Cancer Genetics/Somatic Mutations

There are at least three high-priority expansion biomarkers that should be considered for answering specific questions related to DNA analysis: copy number alterations, single-nucleotide polymorphisms (SNP), and T-cell-receptor (TCR) and B-cell receptor (BCR) deep sequencing. Each of these should be employed as called for in relation to the mechanism of action of the therapy being tested.

Single-Nucleotide Polymorphisms (SNPs)

While still exploratory, germline SNPs that are associated with autoimmune disease may be useful to predict response or adverse events in cancer immunotherapy. One approach is to use SNP arrays to characterize established autoimmune markers. For example, genome-wide association studies have identified hundreds of SNPs associated with autoimmune diseases such as rheumatoid arthritis, lupus, and multiple sclerosis (Gregersen, Diamond, & Plenge, 2012). Immuno-oncology (IO) therapies alter the state of the immune system within the TME, and a major limitation is autoimmune adverse events. SNP genotyping will determine if the genetic predisposition to autoimmune disorders is predictive of response to IO therapy or adverse events. Ninety-five percent of 612 SNPs associated with 21 common autoimmune diseases can be genotyped using a combination of two commercially available SNP chips (MEG and Immune) from Illumina. These chips could be enhanced with additional SNPs associated with less common autoimmune disorders observed as adverse events during IO treatment.

TCR and BCR Deep Sequencing

Advances in genome sequencing technologies have also enabled the development of a new powerful platform for probing the adaptive immune systems (immunosequencing). Millions of TCR or BCR sequences can be read in parallel from a single sample by immunosequencing for the quantification of T- and B-cell clonal response in peripheral blood and tumor. The clinical application of immunosequencing for the diagnosis and monitoring of lymphoid malignancies demonstrated high sensitivity and specificity. The presence of tumor-infiltrated lymphocyte (TIL) correlates with a favorable clinical outcome. Emerging data suggest that both the number of TIL and degree of specific clonal expansions in pretreatment melanoma samples are predictive of response to anti-PD-1 therapy (Tumeh et al., 2014). TCR repertoire in peripheral blood correlates with immune-related adverse events in patients treated with immune checkpoint blockade. Immunosequencing biomarkers have the potential to help guide dose regimens and combination therapies. Moreover, for adoptive T-cell transfer or chimeric antigen receptor T-cell therapy, immunosequencing is used to identify novel tumor antigen/neoantigen-specific TCR and monitor the therapy itself by tracking the injected T cells. Immunosequencing has opened many avenues with the breadth of potential application in immunotherapy.

Module 3b: Transcriptomic Characterization of Microenvironment

Emerging technologies are making significant progress in characterizing the primary and acquired resistance mechanism for patients. Challenges include potential changes in RNA during the formation of single-cell suspensions that are required for current scRNA-seq protocols, low capture efficiency of cellular transcripts (10–15% using 3' poly-A capture), and limited sensitivity that makes detection of low-abundance transcripts unreliable. RNA-seq analysis of single functional cytolytic T cells with various immune phenotype markers provides additional information about the impacts of different molecules on cytolytic function, potentially to explore their correlation with clinical outcome.

Focus of the Project

Single-cell suspensions can be obtained from tumor samples where the tissue is processed with or without enzyme digestion, with a need to establish cell freezing media under a standard operation procedure.

No single marker will serve the purpose of transcriptomic characterization of the TME. Therefore, the main focus should be on comprehensive measurements of multiple baseline and on-therapy markers that are related to response and resistance to IO agents. Some of the currently available readouts include the interferon gamma signature, the cytolysis score, and mesenchymal or stemness tumor phenotype.

Experimental Screening Platforms To Include and Purpose for Each:

- Whole-transcriptome profiling via next-generation sequencing (NGS) is recommended with baseline profiling at a minimum, and longitudinal samples for tumor indications where available are strongly encouraged.

- ▶ Peripheral blood mononuclear cell profiling is also recommended.
- ▶ Application of emerging single-cell characterization techniques are suggested to be explored and incorporated.

Emerging tissue processing approaches such as those that recover single nuclei for RNA-seq provide an opportunity to characterize immune subpopulations with unprecedented specificity. One advantage of single-cell techniques compared with bulk profiling is that the molecular features of rare subpopulations can be extracted and may help to identify novel targets. Another advantage is that one can clearly assess the relative frequencies of the various subpopulations such as T cells, T-regulatory cells, MDSCs, and TAMs.

In addition to providing an opportunity to characterize specific immune subpopulations within the TME, single-cell profiling can resolve cell subpopulations that are obscured by whole-tissue transcriptome profiling as well as their associated gene expression patterns and dynamics, and quantify cellular heterogeneity within a tissue, peripheral blood, fine-needle aspirate, or bone marrow aspirate.

Value Proposition

It is important to characterize the primary and acquired resistance mechanisms for patients who fail to respond to immune checkpoint blockade monotherapy, or transiently respond and then progress afterward. Transcriptomic profiling is one approach to identify these resistance mechanisms and guide combination clinical strategies, and can also be used to assess the impact of drug treatment to identify or validate pharmacodynamics markers of response.

Module 4b: Liquid Biopsy – Circulating Tumor Cells (CTCs), cfRNA, Exosomes

Focus of the Project

For the expansion biomarker module for liquid biopsy, we will look to develop techniques for better analyzing CTCs, cfRNA, and exosomes.

Experimental Screening Platforms To Include and Purpose for Each:

- ▶ Quantitative polymerase chain reaction (qPCR) – research tool that is readily translatable into commercial and regulatory viable *in vitro* diagnostic
- ▶ NGS – RNA-seq – good for biomarker discovery/research, laboratory-developed test approaches; also may be preferred technology in specific settings (e.g., detection of minimal residual disease in certain heme malignancies)
- ▶ Epic Biosciences and Rarecyte CTC platforms – selection agnostic CTC approaches; broader potential across many tumor types
- ▶ Exosome collection and subsequent DNA/RNA sequencing methods

Module 5: Defining the Role of the Microbiome in Modulating Cancer Immunotherapy Responses

Determinants of response to checkpoint blockade are under intense research and are likely to include immunosuppressive status in the TME as well as systemic priming status of the immune system.

Microbiome biomarker development is an active area of research that has already yielded intriguing results that have not only associated microbial population changes with oral, pancreatic, and colon cancer, but may also yield clues regarding the molecular mechanisms linking microbial interactions with these and other types of tumors (Linares, Gustafsson, Baquero, & Martinez, 2006; Schloissnig et al., 2013).

At present, there are no human datasets linking microbiome changes with anti-tumor responses. However, some intriguing recent preclinical studies suggest that the microbiome is required for the anti-tumor activity of anti-PD-L1 and anti-CTLA4, as these antibodies lack their efficacy in mice devoid of microbiota, and the efficacy is transmissible to poor-responder mice via the microbiota. Although we are at a very early stage in this field, these animal studies suggest that systemic immunity is in part regulated by the microbiome.

Value Proposition

Since human data are fundamental to start to address the role of the microbiome in cancer immunotherapy, we propose to stimulate prospective studies in patients undergoing immunotherapy. The principal activity will focus on bacterial communities measurable in fecal samples. Potentially, this project could be expanded to include multiple microbial communities across different mucosal surfaces.

Microbes as Biomarkers

Well-characterized and validated biomarkers of disease can be used for cancer detection and diagnosis, or to measure patient response to therapeutics, and may also provide a rationale for choice of therapy.

The importance of developing microbiome-based patient phenotypes is supported by recent studies demonstrating that when gut bacterial communities are compromised, immunotherapy and standard chemotherapy regimens may lose efficacy (Iida et al., 2013; Viaud et al., 2013). Thus, a detailed knowledge of each cancer patient's unique microbiome could have high translational value to clinical practice since this information could be exploited for the purposes of optimizing individual therapeutic responses, possibly by altering microbial signals to change host metabolic regulation or by developing new metrics for patient stratification based upon matching therapeutic agents with an individual's microbial metabolism or immune profile.

Focus of the Project

Depending on the clinical application, microbiome-based biomarkers may be developed by examining various features and readouts, alone or in combination with existing biomarkers. For example, advanced *in silico* techniques have been used to analyze individual metagenomic profiles as a molecular biomarker that may identify pathogenic or drug-resistance collective phenotypes (Zackular, Rogers, Ruffin, & Schloss, 2014).

Indeed, a current clinical trial (NCT02141945) is testing a metagenomic-based diagnostic tool for patients with colonic neoplasia.

Other strategies have been devised to associate specific tumor/microbe interactions that include the following:

- ▶ Analysis of whole-organism presence/abundance
- ▶ Detection/quantification of biosynthetic products (outer membrane vesicles, miRNA, toxins, lipopolysaccharide [LPS])
- ▶ Detection/quantification of microbial metabolites (short-chain fatty acids [SCFAs], 2-HG, bile acids)
- ▶ Molecular signatures of host responses to altered microbiomes

Thus, colonic hyperpermeability and pro-inflammatory cytokine profiles that are associated with specific bacterial taxa could be used to identify individuals at risk for disease progression or poor therapeutic response.

Potential biomarkers that PACT could expand to test are:

- ▶ Levels of bacterial taxa (16S sequence data)
- ▶ Levels of bacterial metabolites (SCFAs, bile acids, etc.)
- ▶ Levels of bacterial enzymes (β -glucuronidase (GUS), bile acid hydrolases, etc.)
- ▶ Levels of serum LPS, muramyl dipeptide
- ▶ Host inflammatory cytokines/host molecular signatures of dysbiosis

Experimental Screening Platforms To Include and Purpose for Each:

- ▶ Enzyme activity screens (480-well) for detecting bacterial enzyme levels
- ▶ Microarray or enzyme-linked immunosorbent assay for detecting cytokine profiles
- ▶ High-throughput mass spectrometry for detecting bacterial metabolites
- ▶ Quantitative immunohistochemistry for detecting immune checkpoint receptor levels after probiotic treatment

Module 6: Non-Immune Cell Characterization of Tumor Microenvironment (Differentiation, Stroma, Vasculature, Etc.)

Tumor resistance and immune evasion are influenced tremendously by the surrounding nonimmune microenvironment that can include stromal cells, blood vessels, and small particles (e.g., exosomes, ectosomes, microvesicles), cytokines, and enzyme or adhesive properties that are derived from these. These have distinct roles based upon the type of cancer (solid tumor versus hematologic disseminated tumor) and intrinsic driving tumor biology.

Focus of the Project

PACT could use the following as a starting point for expansion biomarker modules:

- ▶ Small particles (exosomes, ectosomes, microvesicles) from blood and the TME.
- ▶ Antibodies that selectively separate mesenchymal stromal cells from tumor and hematopoietic immune cells and strategies to isolate these for single-cell molecular characterization.
- ▶ Markers of blood vessels (i.e., CD34, CD31 and endoglin), effective angiogenesis, and tumor hypoxia and strategies to accurately quantitate these in relevant models.
- ▶ The representative nonimmune cell genes (DNA and RNA) could be used to assess the signature of vasculature, stroma, and other nonimmune cells in the TME. It is of importance to explore their correlation with tumor and immune cell-derived signature in the same tumor, as well as clinical outcome.
- ▶ Baseline serum vascular endothelial growth factor (VEGF) demonstrated the correlation with clinical outcome in melanoma patients treated with CTLA-4 blockade.
- ▶ Combination anti-VEGF with checkpoint blockade showed better clinical response in patients with melanoma and renal cell carcinoma.

Experimental Screening Platforms To Include and Purpose for Each:

As small particles and their contents will be mixed in blood, technologies that separate these based upon distinct antigens expressed by the releasing nonimmune microenvironment cells will be important.

If canine models of spontaneous cancer are chosen to study this, it will be necessary to establish the reagents compatible with exosome (and other small particle separation) and also IHC and separation strategies for other types of stromal cells.

Imaging strategies that allow examination of intracellular exosomes and their trafficking along with adhesive properties of tumor and stromal cells will be important.

Support of a comprehensive center to study this in the setting of spontaneous canine tumors or another large animal model will be needed.

Value Proposition

While features related to tumor vasculature and angiogenesis have been extensively studied and therapeutics directed toward this successfully, our understanding of the other components of the nonimmune microenvironment is at an elemental stage. Furthermore, animal models available to study this are very limited. An opportunity to study these interactions comes potentially from the many solid and hematologic spontaneous mouse models and also companion canine models of cancer where serial sampling of tumors can occur and sufficient blood volume can be obtained to study soluble factors as well. Early clinical data showed that combination immune checkpoint blockade with the agents to overcome nonimmune-cell-derived suppression potentially achieved a synergistic, favorable clinical response.

Appendix 2: Additional Assay Standardization and Harmonization Examples

PDL-1 IHC Comparability Example

An example of a collaboration that addresses comparability of assay approaches across multiple immunohistochemistry (IHC)-based PD-L1 tests is the Blueprint PD-L1 IHC Assay Comparison Project developed by four pharmaceutical companies (Bristol-Myers Squibb, Merck & Co. Inc., AstraZeneca PLC, and Genentech, Inc.) and two diagnostic companies (Agilent Technologies, Inc./Dako Corp and Roche/ Ventana Medical Systems, Inc.) in collaboration with the International Association for the Study of Lung Cancer and the American Association for Cancer Research (AACR). The project aims to cross compare four different diagnostics, including U.S. Food and Drug Administration (FDA)-approved tests, for detection of PD-L1 expression in tumor tissue (Averbuch et al., 2015). The PD-L1 IHC 22C3 pharmDx test was approved as a companion diagnostic to pembrolizumab as a single agent in second-line nonsmall-cell lung cancer (NSCLC). The test was used to determine patient eligibility in a single arm study KEYNOTE 001. The PD-L1 IHC 28-8 pharmDx test was approved by the FDA as a complementary test to another PD-1 inhibitor, nivolumab, in the nonsquamous nonsmall-cell lung cancer (NSCLC) and melanoma patient populations. The scope of the Blueprint Project was to establish technical comparability between the assays. Preliminary results of this effort were presented at the 2016 AACR annual meeting. Analyses from the Blueprint Project confirm that there is high concordance for the two approved PD-L1 diagnostics in NSCLC (American Association for Cancer Research, 2016; Hirsch et al., 2017).

Assay Harmonization Effort Examples

Currently, there are several ongoing initiatives to coordinate and harmonize immunoprofiling efforts including the Human Immunology Project, Minimal Information About T Cell Assays (MIATA), human leukocyte antigen-peptide multimer assays, and others (Britten et al., 2009; Britten et al., 2012; Maecker et al., 2010; Maecker, McCoy, & Nussenblatt, 2012; Mandruzzato et al., 2016).

Other technologies, such as gene expression microarrays, have achieved a reasonable degree of standardization led by consortia such as the Microarray Quality Control (Patterson et al., 2006), the External RNA Controls Consortium (Devonshire, Elaswarapu, & Foy, 2010), and the EMERALD project (Beisvåg et al., 2011).

Another example of assay harmonization to minimize data variability and allow worldwide correlations is the Immunoscore initiative (Galon et al., 2012). Effective large-scale assay harmonization efforts have been conducted for IHC-based immunological assays of immune cell populations in formalin-fixed paraffin-embedded (FFPE) tumor sections. The Immunoscore includes the immune cell density, calculated by numerical quantification of two lymphocyte populations, cytotoxic and memory T cells at the tumor center, and the invasive margin of tumors. This criterion has the potential to establish prognosis of patient clinical outcome,

regardless of the absence of other cancer-associated prognostic markers, such as in early tumor stage (I/II) patients. Importantly, it will need to be validated as a predictor of response for immunotherapy.

Pre-analytical Considerations for Standardization of Key Assays

Pre-analytical processing of samples for diagnostic assays including those used for single-cell immune response assays, such as ELISpot or flow cytometric analysis, includes patient-related factors such as tissue-ischemia time, pretreatment with drugs, dynamic nature of the analyte, and sample heterogeneity. Analyte stability can be affected by the sample collection process including anticoagulants and preservatives used for blood draws, freezing/thawing conditions, time between collection and testing, and storage conditions before processing (Mallone et al., 2011).

IHC, the most widely used platform for biomarker assessment in diagnostic surgical pathology and for retrospective research, is a multistep process that requires standardized conditions for tissue collection, fixation and processing, preparation of the IHC slide, and interpretation of the staining results. IHC-based assays remain important tests as complementary diagnostics and companion diagnostics to assess antigen expression on diagnostic or surgical specimens for selecting patients for specific targeted therapies (e.g., HER2 expression for Herceptin), and more recently PD-L1 measurement as a companion diagnostic for pembrolizumab treatment of NSCLC patients. Published guidelines for measuring established biomarkers such as estrogen receptor, progesterone receptor, and HER2 are available (Hammond et al., 2010). General guidelines, including analyte stability and laboratory quality control, for performing analysis of tissue-based molecular biomarkers have been published (Cree et al., 2014).

Next-generation sequencing tests for tumor mutation analysis, similar to other complex molecular diagnostic tests, should demonstrate adequate analytical performance. It should follow standard operating procedures that specifically address materials and procedures including patient's sample type, method of nucleic acid extraction, as well as technical metrics for nucleic acid quantification and quality, which can negatively impact on sensitivity and reproducibility of the assay (Pant, Weiner, & Marton, 2014; Rehm et al., 2013).

The preparation of intact and pure mRNA is one of the key factors in mRNA gene quantification using gene expression profiling of RNA sequencing. Extraction of nucleic acids and particularly RNA is very sensitive to nucleases. Thus, nuclease free conditions should be implemented to control variability in steps such as sample collection, tissue fixation, and FFPE block handling including sectioning. For the extraction of nucleic acids from the FFPE tumor tissue, a method for the simultaneous isolation of high-quality DNA, RNA, and microRNA as well as protein from the same sample has been developed (Kalmar et al., 2013).

Appendix 3: The PACT Design Team

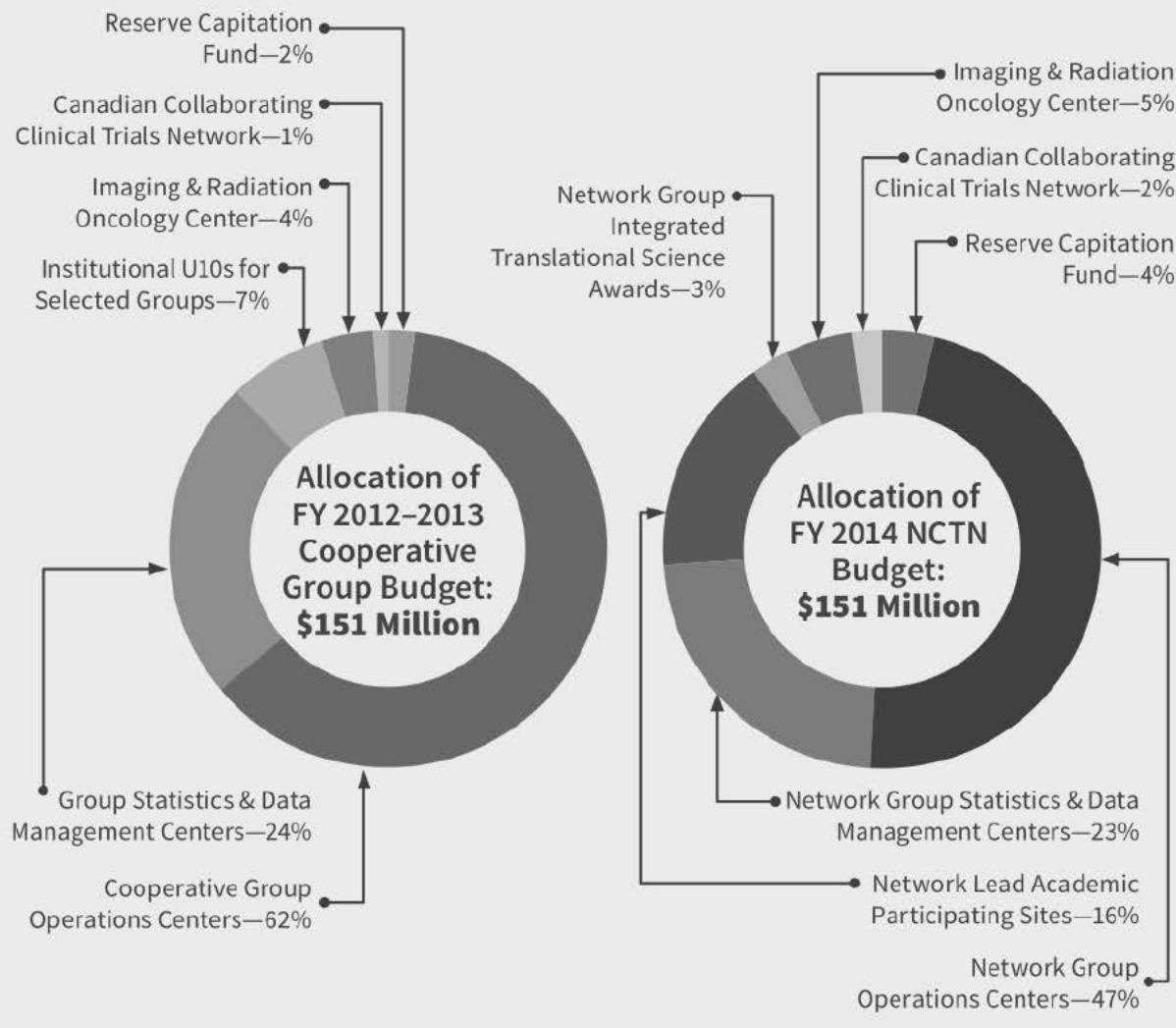
INDUSTRY PARTICIPANTS	Jeff Engelman (Novartis)—Industry Co-Chair		Axel Hoos (GSK)—Industry Co-Chair	
	Bob Abraham (Pfizer)	Matthew Albert (Genentech)	Carl Barrett (AstraZeneca)	Olaf Christensen (EMD)
	Ute Dugan (BMS)	Jeff Ecsedy (Takeda)	Jessie English (EMD)	Howard Fingert (Takeda)
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	Greg Plowman (Lilly)	Chandra Ramanathan (Bayer)	David Reese (Amgen)	Paul Rejto (Pfizer)
	Andrew Schade (Lilly)	Armin Schuler (EMD)	Flavio Solca (B-I)	Jianda Yuan (Merck)
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ACADEMIC PARTICIPANTS	John Byrd (OSU)	Levi Garraway (Broad/Lilly)	Steve Hodi (DFCI)	Patricia LoRusso (Yale)
	Antoni Ribas (UCLA)	Lillian Siu (PMCC)	Mario Sznol (Yale)	Jedd Wolchok (MSKCC)
PACT PROGRAM MANAGEMENT	Stacey Adam (FNIH)	David Wholley (FNIH)		

Appendix 4: Detailed Description of the Cancer Therapy Evaluation Program (CTEP) – National Clinical Trials Network (NCTN)

The NCTN Budget

The overall NCTN budget for these awards is \$151 million. This amount is the same as the total budget provided to the Cooperative Groups for awards in each of fiscal years (FY) 2012 and 2013, despite the substantial reductions in the National Cancer Institute (NCI) budget that resulted from sequestration starting in 2013. What has changed, however, is the distribution of funds to the various components of the NCTN, as compared with the components of the former Cooperative Group program.

The distribution of funds to the Network Group Operations Center grants changed from 62 percent in FY 2012 and 2013 to 47 percent in FY 2014 due to the consolidation of the infrastructures of the Operations and Statistical Centers; funding of new components in the NCTN, including the Lead Academic Participating Sites and Integrated Translational Science Awards; and expansion of the Imaging and Radiology Oncology Group for the entire network. The new system provides for an annual enrollment of about 17,000 patients on interventional trials, a 15 percent reduction compared with about 21,000 enrolled patients in recent years. This reduction is anticipated to occur gradually over 2 to 3 years. To this end, NCI reserved funds to distribute to the NCTN groups later in FY 2014 to accommodate an enrollment of about 21,000 patients.

COMPARISON OF COOPERATIVE GROUP PROGRAM FUNDING AND NCTN PROGRAM FUNDING**Funding Precision Medicine Trials**

NCI believes that reducing the budget of the Network Group Operations Centers will not impede the NCTN's ability to perform important trials. Conducting the new generation of clinical trials requires new technologies and procedures, including tissue collection (fresh biopsy samples are often necessary), advanced DNA and RNA sequencing methods with rapid turnaround times, and complex analytic algorithms to distinguish normal genetic variants from tumor-specific changes. These, in turn, entail new expenses for surgery, interventional radiology, molecular pathology, and bioinformatics that have not typically been a part of clinical trials.

However, although the screening tests may need to be performed on very large numbers of patients to find those whose tumors exhibit the appropriate molecular profile, the numbers of patients required for interventional studies are likely to be smaller than what was required in previous trials.

That is because the patient selection is based on having the target for the new therapy, leading to larger differences in clinical benefit (such as how long patients live overall or live without tumor progression) between the intervention and control groups. Thus, future clinical trials will, in many cases, require fewer numbers of patients due to the selection of patients most likely to benefit from the intervention being tested.

Although screening patients for tumors with specific molecular characteristics may require large numbers of patients, the screening components of studies are less costly than the actual interventional study. Hence, clinical trials in the future are likely to involve screening components, which will be reimbursed at a lower rate, with smaller interventional components that will be reimbursed at higher rates. More precision in patient selection will permit study designs that can aim for larger therapeutic effects and thereby further decrease the size of trials.

Efficiencies in Collaboration

These changes will, however, require the NCTN groups to function differently compared with how they functioned in the previous system. For example, NCTN groups should be able to reduce the costs of conducting trials by sharing resources. If a particular group has many active trials, it may have to decrease the number of new trials it is planning. Groups with fewer active trials can take up those new trials instead. This collaborative approach should allow members of one NCTN group to support trials led by other groups and should afford NCTN members an ability to conduct a full portfolio of trials in the most common cancers.

Because the NCTN has only four U.S. adult groups, with fewer Operations and Statistical Centers that require financial support, some savings are anticipated. This consolidation was planned for over the past several years, and NCI provided \$24 million in funding supplements to the newly consolidated groups to help them absorb the costs of their ongoing trials as well as to fund the integration of their separate infrastructures.

NCI also provided more than \$40 million in other funding supplements to transition all the groups to a common data management system (Medidata Rave®), develop an integrated IT system for the tissue banks, and implement specific precision medicine clinical trials.

Additional Support

For the past several years, NCI has provided significant additional annual support for the Cooperative Groups and will continue to provide these funds for the NCTN, in addition to the grant funding described above. Clinical trials are complex undertakings that require a host of support organizations and funding streams. The new system includes a number of other features that are not included in the NCTN awards but are essential to carrying out the NCTN mission.

The additional support includes:

- ▶ Central Institutional Review Boards, an important component of NCI's clinical trials system that has added speed, efficiency, and uniformity to ethics review.

- ▶ The Cancer Trials Support Unit, an NCI-funded contract that provides clinical investigators and their staff with one-stop online access to NCTN trials and allows investigators to register new patients.
- ▶ A dedicated tissue bank for each Network group funded through a separate NCI award mechanism.
- ▶ The Biomarker, Imaging, and Quality of Life Studies Funding Program, a separate funding stream for NCTN trials that supports correlative science studies on group trials. NCTN groups compete for funds that are specifically reserved annually for this purpose. The availability of dedicated funds greatly facilitates coordination as clinical trials must meet stringent deadlines.
- ▶ In addition, approximately one-quarter of patient accrual on NCTN treatment trials is paid for by the NCI Community Oncology Research Program (NCORP; previously the Community Clinical Oncology Program/Minority-Based Community Clinical Oncology Program). The community hospitals and medical centers participating in the NCORP are reimbursed for accruing patients to NCTN treatment trials by their NCORP awards, not via the NCTN Group Operations award.

ADDITIONAL ANNUAL NCI SUPPORT	
NCI Central IRBs (Adult & Pediatrics)	\$4.5 Million
Cancer Trials Support Unit	\$14.0
Tissue Banks	\$8.6
Biomarker, Imaging, and Quality of Life Studies Funding Program	\$10.0
NCORP Support for NCTN Treatment Trials (Estimated)	\$33.1
\$70.2 Million*	

Other NCI support includes but is not limited to:

- ▶ Operations of common data management system (Medidata Rave®)
- ▶ Clinical trials auditing
- ▶ Drug storage and distribution
- ▶ Regulatory oversight (CTEP IND Studies)

*This is an approximation and is dependent on annual NCI appropriations.

Finally, in addition to these substantial annual expenditures, NCI also subsidizes the NCTN by paying for many other essential clinical trial functions, thereby further reducing costs borne by the Network groups:

- ▶ NCI will pay for the licenses and hosting fees of the electronic, common data management system, called Medidata Rave®, used by all NCTN groups.
- ▶ NCI will oversee a national audit system for NCTN trials.
- ▶ NCI will manage Investigational New Drug applications to the U.S. Food and Drug Administration along with the distribution of these drugs for many NCTN trials.

It is estimated that support for these activities costs NCI approximately \$15 million annually.

<https://www.cancer.gov/research/areas/clinical-trials/nctn/budget>

Appendix 5: Active NIH/NCI Requests for Applications (RFAs) Relevant to PACT

2017

1. CA17-009 Mechanisms of Cancer Drug Resistance and Sensitivity (U54)
2. CA17-006 Cancer Immunologic Data Commons (CIDC) (U24)
3. CA17-005 Cancer Immune Monitoring and Analysis Centers (U24)
4. CA17-013 Advanced Development and Validation of Emerging Biospecimen Science Technologies for Basic and Clinical Cancer Research (R33)

2016

5. CA16-501 Limited Competition: Cancer Immunotherapy Trials Network (CITN)(UM1)

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NIH - 003426

From: Wholley, David (FNIH) [T]
Sent: Mon, 9 Oct 2017 14:59:49 +0000
To: Collins, Francis (NIH/OD) [E];Tabak, Lawrence (NIH/OD) [E];Lowy, Douglas (NIH/NCI) [E];Doroshow, James (NIH/NCI) [E];Myles, Renate (NIH/OD) [E];Baker, Rebecca (NIH/OD) [E]
Cc: Wolinetz, Carrie (NIH/OD) [E];Burklow, John (NIH/OD) [E];Adam, Stacey (FNIH) [T];Meltzer, Abbey (FNIH) [T]
Subject: FW: Partnership to Accelerate Cancer Therapies (PACT)

(b) (4)

Thanks, David

David Wholley
Director, Research Partnerships
Foundation for the National Institutes of Health
(301) 594-6343
fnih.org

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From: (b) (4), (b) (6)
Sent: Monday, October 09, 2017 10:39 AM
To: Wholley, David (FNIH) [T] <dwholley@fnih.org>
Cc: (b) (4), (b) (6)
Subject: Re: Partnership to Accelerate Cancer Therapies (PACT)

David (b) (4)
(b) (4)

(b) (4)

Best regards,

Dave

On Oct 9, 2017, at 5:47 AM, Wholley, David (FNIH) [T] <dwholley@fnih.org> wrote:

I will call you a 730 PT

Sent from my BlackBerry 10 smartphone.

From: (b) (4), (b) (6)

Sent: Sunday, October 8, 2017 11:18 PM

To: Wholley, David (FNIH) [T]

Cc: (b) (4), (b) (6); Collins, Francis (NIH/OD) [E]; Baker, Rebecca (NIH/OD) [E]

Subject: Re: Partnership to Accelerate Cancer Therapies (PACT)

Hi David,

Any time between 7:30-9 PT would be good, if you are available.

Please call my cell phone: (b) (6)

Look forward to talking to you -

(b) (4), (b)
(6)

On Oct 8, 2017, at 8:01 PM, Wholley, David (FNIH) [T] <dwholley@fnih.org> wrote:

Hi David, is there a good time for me to call you tomorrow?

Sent from my BlackBerry 10 smartphone.

From: (b) (4), (b) (6)

Sent: Sunday, October 8, 2017 6:10 PM

To: Collins, Francis (NIH/OD) [E]

Cc: Wholley, David (FNIH) [T]; Baker, Rebecca (NIH/OD) [E]; (b) (4), (b) (6)

Subject: Re: Partnership to Accelerate Cancer Therapies (PACT)

Dear Francis,

(b) (4)

On Oct 2, 2017, at 2:38 PM, Collins, Francis (NIH/OD) [E] (b) (6) wrote:

Dear (b),
(4)

I wanted to give you an update on the Partnership to Accelerate Cancer Therapies (PACT). As you may recall NIH worked with FNIH, FDA, and 14 pharmaceutical companies (b) (4) earlier this year to plan a public-private partnership that would help coordinate the development of standardized biomarkers and assays needed to conduct trials of new cancer immunotherapies and combination therapies. The resulting plan builds on a \$160 million investment by NCI over 5 years in core laboratory and database infrastructure with (b) (4) to expand the number of novel markers, assays, and types of data that can be developed.

(b) (4)

(b) (4) As a result, we now have eight companies pledged to support PACT, and will be holding an announcement at the National Press Club here in Washington on October 12 with all of the participants.

(b) (4)

(b) (4) Might you be willing to reconsider joining PACT, given where things now stand? It would be great to know before Oct. 12th so we can include you in the planning for the announcement.

(b) (4)

Warm regards, Francis

<Updated PACT Executive Summary 092617.docx>

From: Wholley, David (FNIH) [T]
Sent: Tue, 10 Oct 2017 13:55:12 +0000
To: Collins, Francis (NIH/OD) [E]
Cc: Baker, Rebecca (NIH/OD) [E];Adam, Stacey (FNIH) [T]
Subject: FW: Partnership to Accelerate Cancer Therapies (PACT)

(b) (4)

David Wholley
Director, Research Partnerships
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From: (b) (4), (b) (6)
Sent: Tuesday, October 03, 2017 10:45 PM
To: Collins, Francis (NIH/OD) [E] (b) (6)
Cc: Wholley, David (FNIH) [T] <dwholley@fnih.org>; Baker, Rebecca (NIH/OD) [E]
(b) (6)
Subject: Re: Partnership to Accelerate Cancer Therapies (PACT)

Francis

I will look into it ,check with our division heads and let you know

Best
(b) (4), (b)
(6)

Envoyé de mon iPhone

Le 3 oct. 2017 à 18:29, Collins, Francis (NIH/OD) [E] (b) (6) a écrit :

(b) (4)

(b) (4)



<Updated PACT Executive Summary 092617.docx>

From: Wholley, David (FNIH) [T]
Sent: Tue, 3 Oct 2017 15:10:29 +0000
To: Collins, Francis (NIH/OD) [E]
Subject: FW: Partnership to Accelerate Cancer Therapies
Attachments: Updated PACT Executive Summary 092617.docx

(b) (4)

David Wholley
Director, Research Partnerships
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fnih.org

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From: Wholley, David (FNIH) [T]
Sent: Tuesday, October 03, 2017 10:10 AM
To: Collins, Francis (NIH/OD) [E] (b) (6)
Subject: Partnership to Accelerate Cancer Therapies

Dear (b).
(4)

It has been a while since we spoke about this, but I wanted to ask you for a favor regarding another public-private partnership we have been developing: the Partnership to Accelerate Cancer Therapies (PACT). As you might recall, we've spent the last 15 months or so working with FNIH, FDA, and multiple pharmaceutical companies to plan a partnership that would help coordinate the development of standardized biomarkers and assays needed to conduct trials of new cancer immunotherapies and combination therapies. The resulting plan builds on a \$160 million investment by NCI over 5 years in core laboratory and database infrastructure with (b) (4) to expand the number of novel markers, assays, and types of data that can be developed.

(b) (4)

The driving factor is that FNIH now has 8-9 companies pledged to support PACT, and that with encouragement from the White House we have committed to hold an announcement at the National Press Club downtown on October 12 (modeled on the announcements held for the Biomarkers Consortium and AMP). (b) (4)

(b) (4)

I have attached a 2-page summary of PACT for reference, but please let me know if you have any additional questions.

Warm regards, Francis

<Updated PACT Executive Summary 092617.docx>

Executive Summary

Recent advances in cancer treatment have offered the prospect of greatly enhanced outcomes, prolonged survival, and cure for some patients. Much of the recent success has been driven by the development of new immuno-oncology (IO) agents, leading to an explosion of translational research as well as investment in the field. To date, however, the improvements in outcomes and cure generated by the monotherapies of these agents are possible only for a minority of patients, and emerging data demonstrate that the greatest impact on cancer treatment will be achieved by combinations of multiple IO agents or of IO and non-IO agents. The successful pursuit of these combination therapies is complicated, however, by the sheer numbers of possible combinations, by high biologic complexity, and by the need for new translational biomarkers and assays to guide which patients should receive which combinations. These challenges are further compounded by the novelty and intensely competitive nature of the IO field, which has encouraged fragmented and at times duplicative research approaches.

To solve these challenges, a systematic cross-sector effort is required to identify and develop robust, standardized biomarkers and related clinical data that support the selection and testing of promising therapeutic combinations. The magnitude of this task and the substantial current knowledge gaps within the field make it unlikely a single stakeholder can execute such a mission alone. As a part of its support of the Cancer Moonshot, the National Institutes of Health (NIH) has proposed a 5-year, ~\$210 million precompetitive public-private research collaboration called the Partnership for Accelerating Cancer Therapies (PACT) to enable achievement of these goals. The initial strategic plan for PACT has been developed through a process led by the Foundation for the NIH (FNIH) with input from 42 key opinion leaders in the cancer field, encompassing representatives from the National Cancer Institute (NCI), U.S. Food and Drug Administration (FDA), academia, and 15 industry partners—AbbVie, Amgen, AstraZeneca, Bayer, Boehringer- Ingelheim, BMS, EMD Serono, Genentech, GSK, Lilly, Merck, Novartis, Pfizer, PhRMA, and Takeda.

PACT aims to accelerate the development of effective combination therapies by enabling critical clinical investigations not covered by others, coordinating development of new biomarkers, filling knowledge gaps, and integrating information from multiple sources.

PACT will facilitate robust, systematic, and uniformly conducted clinical testing of basic biomarkers that enable researchers and clinicians to better understand the mechanisms of response and resistance to treatment strategies. PACT will provide a systematic approach to immune and related oncology biomarker investigation in clinical trials by providing standardized biomarker modules, which can be utilized within the PACT programs and across the research community. These modules allow for (a) consistent generation of data, (b) access to uniform and harmonized assays to support data reproducibility, (c) comparability of data across trials, and (d) discovery/validation of new biomarkers for combination immunotherapies and related combinations. Specific elements of the program include the following:

- Providing a set of basic biomarker modules for uniform clinical application.
- Establishing a network of 3–5 core laboratories to coordinate, conduct, validate, and standardize biomarker assays. Funding the development of standardized biomarkers for immunoprofiling and exploratory biomarker assays of high relevance.
- Incorporating biomarkers and data collection standards into trials prioritized through PACT and coordinating their adoption broadly across the IO research community.
- Creating a comprehensive database that integrates biomarker and clinical data to enable pre-competitive correlative biomarker analyses.

PACT will also work to provide scientific coordination by facilitating information sharing by all stakeholders to better coordinate clinical/translational oncology programs, align investigative approaches, avoid duplication of effort, share resources, and enable more relevant high-quality trials to be conducted. This will include active outreach to other IO research efforts on an ongoing basis.

The core laboratory, assay development, and database functions required will be built on a solid base of research infrastructure and academic grants funded by NCI. Fortunately, NCI released several Requests for Applications (RFAs) in November 2016 that are highly germane to the core goals of PACT. Based largely on existing funding from the Precision Oncology Initiative, with additional planned Cancer Moonshot funding, the NCI plans to contribute ~\$160 million in funding over 5 years beginning in Fall 2017 for a number of Cancer Immune Monitoring and Analysis Centers (CIMACs), a Cancer Immunologic Data Commons (CIDC), and several related initiatives that create integrated multidisciplinary research cores with basic, translational, and computational expertise. Although currently limited as to the number of sites, assays, and data types supported, these grants provide a “shovel ready” foundation for the core lab and database functions required by PACT, particularly when combined with NCI’s recently announced Formulary initiative and its existing national clinical trials network and genomic data management programs.

In addition to supporting these resources, PACT will coordinate and standardize the use of existing biomarker assays so that they can be used efficiently in clinical trials of new medicines. These assays can be conducted in trials outside PACT yet channel data into the PACT database, provided the assays are performed to PACT standards.

The additional ~\$50 million/5 years required to meet the baseline PACT goals will be raised from the private sector through FNIH. These funds will be used to enhance these NCI efforts with funds to be disbursed through FNIH contracts where appropriate. Additional funds may be sought later for future projects of interest to further PACT partnerships and goals.

A joint governance structure will maintain close involvement by all partners in key decisions, consisting of:

- An operationally focused PACT Joint Steering Committee (JSC) to direct the research plan and ensure adherence to project milestones
- A PACT Executive Committee (EC) to provide strategic direction, communication with partner leadership, and resolution of policy issues.

Voting participation in the JSC and EC will be split 50/50 between government and private sector partners.

All PACT data will be released publicly as promptly and broadly as possible in keeping with NIH's mission and policy, though also dependent on restrictions in underlying clinical trial and grant agreements. Where feasible, PACT participants will have early access to data, but consistent with these restrictions.

The value proposition for PACT stakeholders, for the oncology field, and for patients will be considerable, providing immediate:

- Access to standardized immune biomarker modules, enabling a systematic and uniform analytical approach across trials
- Access to databases of pre-competitive biomarker analyses, accelerating hypothesis testing and decision-making
- Access to core development laboratories and facilities with standardized analysis platforms, procedures, and best practices, working with regulatory agencies to ensure quality evidence and documentation that enable potential registration and labeling
- Opportunity to drive new collaborations resulting from PACT insights and contribute to improving cure rates for patients under the goals of the Cancer Moonshot Initiative

The total private sector commitment of ~\$50 million will require an annual requested contribution over 5 years of between \$1 million per year for 5 years from each company. With confirmed partners, FNIH will reconvene the scientific leads to develop a final research plan, including detailed project plans and go/no-go milestones. Given the sense of urgency in addressing patient needs, the timing of NIH funding, and the rapid pace of progress in the field, formal launch of PACT is being targeted for Q1 of 2018.

From: Wholley, David (FNIH) [T]
Sent: Wed, 6 Dec 2017 01:18:56 +0000
To: Collins, Francis (NIH/OD) [E];Tabak, Lawrence (NIH/OD) [E];Volkow, Nora (NIH/NIDA) [E];Stein, Jack (NIH/NIDA) [E];Koroshetz, Walter (NIH/NINDS) [E];Porter, Linda (NIH/NINDS) [E];Wolinetz, Carrie (NIH/OD) [E];Baker, Rebecca (NIH/OD) [E]
Subject: FW: Proposed agenda for Opioids Partnership F2F next week

Thoughts? Happy to make changes. By the way, I don't think our budgeting segment is going to address actual estimates at this point—too early in most cases—but will rather discuss strategies for coming to such general estimations in the white paper writing process.

From: Chin, Bill [mailto:Chin@phrma.org]
Sent: Tuesday, December 5, 2017 5:47 PM
To: Wholley, David (FNIH) [T] <dwholley@fnih.org>
Cc: Baker, Rebecca (NIH/OD) [E] (b) (6); Biarnes, Michael (FNIH) [T] <mbiarnes@fnih.org>; Menetski, Joseph (FNIH) [T] <jmenetski@fnih.org>; Moscicki, Richard <rmoscicki@phrma.org>
Subject: RE: Proposed agenda for Opioids Partnership F2F next week

David, Two thoughts. First, on 12/13 you have scheduled a session entitled, "Focus Area B: Refinement and Budgeting." But there is not analogous session for Focus Area A. Second, I think you should let PhRMA join Francis in the Introduction to ensure the optics reflect the PPP. You don't even need to list either me or Rich but one of us should welcome everyone and particularly get a chance to thank the industry members for their participation. My two cents. Bill

From: Wholley, David (FNIH) [T] [mailto:dwholley@fnih.org]
Sent: Tuesday, December 05, 2017 1:31 PM
To: Chin, Bill
Cc: Baker, Rebecca (NIH/OD) [E]; Biarnes, Michael (FNIH) [T]; Menetski, Joseph (FNIH) [T]
Subject: Proposed agenda for Opioids Partnership F2F next week

Bill, please see the attached, result of our conversations with the NIH group so far, but pending input from the co-chairs and finalization. Please let me know if anything looks amiss.

David

We've moved! Please find our new address below.

David Wholley
Director, Research Partnerships
Foundation for the National Institutes of Health
(301) 594-6343
fnih.org

11400 Rockville Pike Suite 600 North Bethesda, MD 20852

Learn more about the FNIH in our 2016 Annual Report: fnih.org/AnnualReport.

From: Wholley, David (FNIH) [T]
Sent: Thu, 21 Dec 2017 00:16:14 +0000
To: Volkow, Nora (NIH/NIDA) [E];Stein, Jack (NIH/NIDA) [E]
Cc: Koroshetz, Walter (NIH/NINDS) [E];Collins, Francis (NIH/OD) [E];Baker, Rebecca (NIH/OD) [E];Porter, Linda (NIH/NINDS) [E];Tabak, Lawrence (NIH/OD) [E]
Subject: FW: Invitation to Public Workshop: Strategies for Promoting the Safe Use and Appropriate Prescribing of Prescription Opioids

FYI

From: Adam, Stacey (FNIH) [T]
Sent: Monday, December 18, 2017 3:00 PM
To: Menetski, Joseph (FNIH) [T] <jmenetski@fnih.org>; Wholley, David (FNIH) [T] <dwholley@fnih.org>; Biarnes, Michael (FNIH) [T] <mbiarnes@fnih.org>
Subject: FW: Invitation to Public Workshop: Strategies for Promoting the Safe Use and Appropriate Prescribing of Prescription Opioids

Thought this might be interesting to you all.

Stacey J. Adam, Ph.D.
Scientific Program Manager, Cancer
Direct: (301) 435-8364 | Mobile: [REDACTED] (b) (6)

From: Duke-Margolis Center for Health Policy [<mailto:margolisevents@duke.edu>]
Sent: Monday, December 18, 2017 12:37 PM
To: Adam, Stacey (FNIH) [T] <sad'am@fnih.org>
Subject: Invitation to Public Workshop: Strategies for Promoting the Safe Use and Appropriate Prescribing of Prescription Opioids



The Duke-Margolis Center for Health Policy will be convening a public workshop in Washington, DC, on **February 15, 2018**, entitled **Strategies for Promoting the Safe Use and Appropriate Prescribing of Prescription Opioids**.

The meeting will be held from **9 a.m. to 4:15 p.m. EST** at the **National Press Club**, 529 14th Street NW, 13th Floor, Washington, DC 20045.

The current epidemic of opioid misuse, opioid use disorder (OUD), and opioid-related overdose remains a growing public health crisis. In support of efforts by the U.S Food and Drug Administration (FDA) to reduce the impact of opioid misuse on public health, this public workshop will examine interventions and tools being utilized by policymakers, healthcare providers, health systems, payers, and pharmacy benefit managers to ensure the safe and appropriate prescribing of opioids. These approaches may include prescribing guidelines, utilization of Prescription Drug Monitoring Programs (PDMPs), screening and risk-assessment

tools, and other health system and payer strategies to manage opioid access and improve patient safety.

Through a cooperative agreement with the FDA, the Duke-Margolis Center will host a public workshop on February 15, 2018 to:

- Examine the landscape of health system and payer interventions to promote safe and appropriate prescribing of opioids.
- Discuss how health systems and payers are using data and health IT tools to support interventions.
- Discuss how health system approaches were implemented, barriers to their adoption, and potential unintended consequences of adoption.
- Discuss how to build an evidence base to support existing health system and payer interventions as well as how success may be defined and measured.

While this project is supported through a cooperative agreement with FDA, the views expressed in the accompanying documents are those of the participants in attendance, and do not necessarily reflect the official positions and policies of the Department of Health and Human Services, or imply endorsements by the U.S. Government or other organizations.

To find more event information and to register, please click [here](#). Note that in person attendance is limited, so please register at your earliest convenience.

More information on the Duke-Robert J. Margolis, MD, Center for Health Policy can be found on our website at www.healthpolicy.duke.edu.

If you no longer want to receive emails from the Duke-Robert J. Margolis, MD, Center for Health Policy, please [Opt-Out](#)

From: Wholley, David (FNIH) [T]
Sent: Tue, 11 Apr 2017 16:57:10 -0400
To: Hodes, Richard (NIH/NIA) [E];Rodgers, Griffin (NIH/NIDDK) [E];Katz, Stephen I. (NIH/NIAMS) [E]
Subject: FW: Lon Cardon functional validation proposal--your thoughts requested
Attachments: AMP functional downstream opportunities cardon vallance (002).pdf, Dolsten-Collins comments on Cardon proposal 3-16-17.docx

Richard, Griff, Steve:
FYI, David

From: Wholley, David (FNIH) [T]
Sent: Tuesday, April 11, 2017 4:55 PM
To: 'Hodge, Martin' (Martin.Hodge@pfizer.com) <Martin.Hodge@pfizer.com>; Ryan, Laurie (NIH/NIA) [E] [REDACTED] (b) (6) 'Melissa K Thomas' <thomas_melissa_k@lilly.com>; Smith, Philip (NIH/NIDDK) [E] [REDACTED] (b) (6); Carter, Robert (NIH/NIAMS) [E] [REDACTED] (b) (6); Decker, Mike (michael.w.decker@abbvie.com) <michael.w.decker@abbvie.com>
Cc: Canet-Aviles, Rosa (FNIH) [T] <rcanet-aviles@fnih.org>; Hoffmann, Steve (FNIH) [T] <shoffmann@fnih.org>; Vardanian, Lilit (FNIH) [T] <lvardanian@fnih.org>; Melencio, Cheryl (FNIH) [T] <cmelencio@fnih.org>; Morgan, Emily (FNIH) [T] <emorgan@fnih.org>; Menetski, Joseph (FNIH) [T] <jmenetski@fnih.org>
Subject: Lon Cardon functional validation proposal--your thoughts requested

Dear AMP Steering Committee Co-Chairs:

I wanted to let you know first of all that following some discussions at the HEVER meeting this past weekend, Paul Stoffels, the Chief Scientific Officer at Johnson & Johnson, has graciously agreed to replace Francis Cuss on the AMP Executive Committee as an industry representative. Paul is also a member of the FNIH Board of Directors; we're very excited to have him on the AMP team!

(b) (5)



(b) (5)



(b) (5) Could I ask that you think about the proposal and comments (discuss with your Steering Committees if you think appropriate) and share your views with me via email by Friday May 2? I will collate your responses and feed them back to the

EC for discussion thereafter. I have informed our FNIH Scientific Program and Project Managers about this so they can assist you in this if needed.

Thank you,

David Wholley
Director, Research Partnerships
Foundation for the National Institutes of Health

From: Wholley, David (FNIH) [T]
Sent: Tue, 11 Apr 2017 16:59:16 -0400
To: Stoffels, Paul [JJCUS]
Cc: Collins, Francis (NIH/OD) [E];Dolsten, Mikael;Jan Lundberg;Tabak, Lawrence (NIH/OD) [E]
Subject: FW: Lon Cardon functional validation proposal--your thoughts requested
Attachments: AMP functional downstream opportunities cardon vallance (002).pdf, Dolsten-Collins comments on Cardon proposal 3-16-17.docx

Paul:

See below, fyi. You will see the issue mentioned in the Extended EC notes I sent you, but not what has occurred since. Happy to answer any questions or hear your thoughts.

David

From: Wholley, David (FNIH) [T]
Sent: Tuesday, April 11, 2017 4:55 PM
To: 'Hodge, Martin' (Martin.Hodge@pfizer.com) <Martin.Hodge@pfizer.com>; Ryan, Laurie (NIH/NIA) [E] (b) (6) 'Melissa K Thomas' <thomas_melissa_k@lilly.com>; Smith, Philip (NIH/NIDDK) [E] (b) (6); Carter, Robert (NIH/NIAMS) [E] (b) (6); Decker, Mike (michael.w.decker@abbvie.com) <michael.w.decker@abbvie.com>
Cc: Canet-Aviles, Rosa (FNIH) [T] <rcanet-aviles@fnih.org>; Hoffmann, Steve (FNIH) [T] <shoffmann@fnih.org>; Vardanian, Lilit (FNIH) [T] <lvardanian@fnih.org>; Melencio, Cheryl (FNIH) [T] <cmelencio@fnih.org>; Morgan, Emily (FNIH) [T] <emorgan@fnih.org>; Menetski, Joseph (FNIH) [T] <jmenetski@fnih.org>
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Thank you,

David Wholley
Director, Research Partnerships
Foundation for the National Institutes of Health

From: Wholley, David (FNIH) [T]
Sent: Tue, 6 Jun 2017 15:04:50 -0400
To: Collins, Francis (NIH/OD) [E]
Subject: FW: Materials for AMP EC Pre-Call tomorrow AM
Attachments: AMP functional validation proposal and responses 5-31-17.docx
Importance: High

Hi Francis: Did you get a chance to look at this over the weekend? Is it OK to send it to the other EC members? I'd like to give them a little extra time to read and digest it before next Monday's EC call. Thanks, David

From: Wholley, David (FNIH) [T]
Sent: Wednesday, May 31, 2017 6:46 PM
To: Collins, Francis (NIH/OD) [E] (b) (6)
Cc: Canet-Aviles, Rosa (FNIH) [T] <rcanet-aviles@fnih.org>; Hoffmann, Steve (FNIH) [T] <shoffmann@fnih.org>; Vardanian, Lilit (FNIH) [T] <lvardanian@fnih.org>; Melencio, Cheryl (FNIH) [T] <cmelencio@fnih.org>; Wood, Gretchen (NIH/OD) [E] (b) (6); Di Mantova, Emma (NIH/OD) [E] (b) (6); Boskent, Celeste (NIH/OD) [E] (b) (6); NIHDirectorMeetings <NIHDirectorMeetings@mail.nih.gov>; Gadbois, Ellen (NIH/OD) [E] (b) (6); Lea, Allison (NIH/OD) [E] (b) (6); Tabak, Lawrence (NIH/OD) [E] (b) (6)
Subject: Materials for AMP EC Pre-Call tomorrow AM
Importance: High

Francis:

Here are the materials for tomorrow's (early) morning AMP EC pre-call:

- Draft meeting slides
- Minutes from Feb. 27 meeting
- Latest attendee roster (attendance overall looks promising)

I have also just finalized a summary document containing the collated responses from the three existing AMP programs (b) (5) validation proposal. Much of the text appears individually in the AMP EC slides, however the document contains some additional text. I would appreciate you taking a look at it before we send it to the other EC members.

I apologize for the unusually late timing on sending these: tomorrow's pre-call is a little in advance of when we usually do these, so there were more than usual late additions to the slides, in addition to the need to incorporate comments on (b) (5) response document.

Thanks,
David

From: Wholley, David (FNIH) [T]
Sent: Wed, 18 Oct 2017 21:23:46 +0000
To: Collins, Francis (NIH/OD) [E];Tabak, Lawrence (NIH/OD) [E];Volkow, Nora (NIH/NIDA) [E];Koroshetz, Walter (NIH/NINDS) [E];Stein, Jack (NIH/NIDA) [E];Porter, Linda (NIH/NINDS) [E];Baker, Rebecca (NIH/OD) [E];Wolinetz, Carrie (NIH/OD) [E]
Cc: Menetski, Joseph (FNIH) [T];Biarnes, Michael (FNIH) [T]
Subject: FW: New PPPs for pain meds and OUD treatment

All: As promised from my conversation on Monday with Janet Woodcock. Should these folks be invited to Friday's call? If so, should Rebecca be the one to let Bill Chin know? Thanks, David

David Wholley
Director, Research Partnerships
Foundation for the National Institutes of Health
(301) 594-6343
fnih.org

Learn more about the FNIH in our *2016 Annual Report*: fnih.org/AnnualReport.

From: Hertz, Sharon H [REDACTED] (b) (6)
Sent: Wednesday, October 18, 2017 4:59 PM
To: Wholley, David (FNIH) [T] <dwholley@fnih.org>
Cc: Winchell, Celia J (FDA/CDER) [REDACTED] (b) (6); Fields, Ellen (FDA/CDER) [REDACTED] (b) (6)
Subject: New PPPs for pain meds and OUD treatment

Hi,

After discussing this with Dr. Woodcock, I am reaching out to let you know that Ellen Fields will be participating as the primary representative for the new pain meds PPP and Celia Winchell for the OUD treatment PPP. Allison Lin will also be participating from our division.

Thank you,
Sharon

Sharon Hertz, MD
Division Director
Division of Anesthesia, Analgesia, and Addiction Products
FDA/CDER
HFD-170, WO 22, Rm [REDACTED] (b) (6)
10903 New Hampshire Ave.
Silver Spring, MD 20993

[REDACTED] (b) (6)
301 796-7413 Fax

NIH - 003457

From: Wholley, David (FNIH) [T]
Sent: Fri, 7 Apr 2017 22:51:07 -0400
To: Collins, Francis (NIH/OD) [E]
Subject: FW: Next Steps in the development of the AMP PD partnership
Attachments: image001.png
Importance: High

Yesss! I don't know whether you want [(b) (4) to surprise you or not, but great news...

From: [(b) (4), (b) (6)]
Sent: Friday, April 07, 2017 7:37 PM
To: Wholley, David (FNIH) [T] <dwholley@fnih.org>
Subject: Re: Next Steps in the development of the AMP PD partnership

David --
We're in!

[(b) (4)]

Sent from my iPhone

On Apr 3, 2017, at 11:01 AM, [(b) (4), (b) (6)] wrote:

David,
I should have an answer for you by the end of the week. [(b) (4)] is aware.
Best,
[(b) (4)]

From: Wholley, David (FNIH) [T] [mailto:dwholley@fnih.org]
Sent: Monday, April 03, 2017 10:59 AM
To: [(b) (4), (b) (6)] /US; Canet-Aviles, Rosa (FNIH) [T]
Subject: Re: Next Steps in the development of the AMP PD partnership

[(b) (4)]

Thanks, David

Sent from my BlackBerry 10 smartphone.

From: [(b) (4), (b) (6)]
Sent: Wednesday, March 29, 2017 11:53 AM
To: Canet-Aviles, Rosa (FNIH) [T]; [(b) (4), (b) (6)]

Cc: Wholley, David (FNIH) [T]; [REDACTED] (b) (4), (b) (6)

Subject: RE: Next Steps in the development of the AMP PD partnership

Hi, Rosa --

(b) (4)

From: Canet-Aviles, Rosa (FNIH) [T] [<mailto:rcanet-aviles@fnih.org>]

Sent: Wednesday, March 29, 2017 10:16 AM

To: [REDACTED] (b) (4), (b) (6)

Cc: Wholley, David (FNIH) [T]; [REDACTED] (b) (4), (b) (6)

Subject: Next Steps in the development of the AMP PD partnership

Importance: High

Dear [REDACTED] (b),
(4)

I hope you are doing very well. It was a pleasure having a chance to meet you in person during the NAS Workshop on Biomarkers or Neuroinflammation last week.

(b) (4)

Best regards,
Rosa

Rosa M Canet-Avilés, PhD
Scientific Program Manager, Neuroscience
Research Partnerships
Foundation for the National Institutes of Health

9650 Rockville Pike | Bethesda, MD 20814 | www.fnih.org
Direct (301) 402-5346 | Cell phone [REDACTED] (b) (6) | rcanet-aviles@fnih.org
<image001.png>





From: Wholley, David (FNIH) [T]
Sent: Sat, 8 Apr 2017 10:57:24 -0400
To: Collins, Francis (NIH/OD) [E]
Subject: Fw: Next Steps in the development of the AMP PD partnership
Attachments: Slide .pptx

I stand corrected
Sent from my BlackBerry 10 smartphone.

From: Sutherland, Margaret (NIH/NINDS) [E] (b) (6)
Sent: Saturday, April 8, 2017 10:48 AM
To: Wholley, David (FNIH) [T]; Canet-Aviles, Rosa (FNIH) [T]; Collins, Francis (NIH/OD) [E]
Subject: RE: Next Steps in the development of the AMP PD partnership

- Coordination of clinical data assessments and biosample collection across Parkinson's disease biomarker cohorts (MJFF, NINDS and Harvard Biomarker Study) enables integration of clinical data and biomarker analysis across large longitudinal cohorts.
- Biofluid samples from standardized longitudinal collection across a 3-5 year timeframe for biomarker discovery, replication, validation **are currently available** from over 3,000 PD patients and 1,000 healthy control subjects

From: Wholley, David (FNIH) [T]
Sent: Saturday, April 08, 2017 10:35 AM
To: Sutherland, Margaret (NIH/NINDS) [E] (b) (6) Canet-Aviles, Rosa (FNIH) [T]
<rcanet-aviles@fnih.org>
Subject: Fw: Next Steps in the development of the AMP PD partnership

Feel free to send the answer directly. FC's presentation is sometime today. I will look too

Sent from my BlackBerry 10 smartphone.

From: Collins, Francis (NIH/OD) [E] (b) (6)
Sent: Saturday, April 8, 2017 5:59 AM
To: Wholley, David (FNIH) [T]
Subject: RE: Next Steps in the development of the AMP PD partnership

Just reviewing the white paper and there's one thing I don't see – what's the total number of patients (roughly) in the cohorts that are part of Project 2?

From: Wholley, David (FNIH) [T]
Sent: Friday, April 07, 2017 10:51 PM
To: Collins, Francis (NIH/OD) [E] (b) (6)
Subject: FW: Next Steps in the development of the AMP PD partnership
Importance: High

Yesss! I don't know whether you want (b) (4) to surprise you or not, but great news...

From: (b) (4), (b) (6)
Sent: Friday, April 07, 2017 7:37 PM

To: Wholley, David (FNIH) [T] <dwholley@fnih.org>
Subject: Re: Next Steps in the development of the AMP PD partnership

David --
We're in!

(b)
(4)

Sent from my iPhone

On Apr 3, 2017, at 11:01 AM, [REDACTED] (b) (4), (b) (6).
wrote:

David,
I should have an answer for you by the end of the week. (b) (4) is aware.
Best,
[REDACTED]
(b)
(4)

From: Wholley, David (FNIH) [T] [<mailto:dwholley@fnih.org>]
Sent: Monday, April 03, 2017 10:59 AM
To: [REDACTED] (b) (4), (b) (6); Canet-Aviles, Rosa (FNIH) [T]
Subject: Re: Next Steps in the development of the AMP PD partnership

[REDACTED] (b) (4)

Thanks, David

Sent from my BlackBerry 10 smartphone.

From: [REDACTED] (b) (4), (b) (6)
Sent: Wednesday, March 29, 2017 11:53 AM
To: Canet-Aviles, Rosa (FNIH) [T]; [REDACTED] (b) (4), (b) (6)
Cc: Wholley, David (FNIH) [T]; [REDACTED] (b) (4), (b) (6)
Subject: RE: Next Steps in the development of the AMP PD partnership

Hi, Rosa --

[REDACTED] (b) (4)

From: Canet-Aviles, Rosa (FNIH) [T] [<mailto:rcanet-aviles@fnih.org>]
Sent: Wednesday, March 29, 2017 10:16 AM
To: [REDACTED] (b) (4), (b) (6)
Cc: Wholley, David (FNIH) [T]; [REDACTED] (b) (4), (b) (6)

Subject: Next Steps in the development of the AMP PD partnership

Importance: High

Dear [REDACTED] (b),
(4)

I hope you are doing very well. It was a pleasure having a chance to meet you in person during the NAS Workshop on Biomarkers or Neuroinflammation last week.

(b) (4)



Best regards,
Rosa

Rosa M Canet-Avilés, PhD
Scientific Program Manager, Neuroscience
Research Partnerships
Foundation for the National Institutes of Health

9650 Rockville Pike | Bethesda, MD 20814 | www.fnih.org
Direct (301) 402-5346 | Cell phone [REDACTED] (b) (6) | rcanet-aviles@fnih.org
<image001.png>

From: Wholley, David (FNIH) [T]
Sent: Fri, 1 Dec 2017 14:07:56 +0000
To: Collins, Francis (NIH/OD) [E]
Cc: Tabak, Lawrence (NIH/OD) [E];Wolinetz, Carrie (NIH/OD) [E]
Subject: FW: NYTimes.com: Gifts Tied to Opioid Sales Invite a Question: Should Museums Vet Donors?

distribute to team

Sent by rbalthaser@yahoo.com:

The New York Times



Gifts Tied to Opioid Sales Invite a Question: Should Museums Vet Donors?

BY COLIN MOYNIHAN

The issue of how museums raise their money has resurfaced in the case of the Sacklers, a family of philanthropists whose company developed OxyContin.

Or, copy and paste this URL into your browser: <https://nyti.ms/2kewSzc>

To ensure delivery to your inbox, please add nytdirect@nytimes.com to your address book.

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From: Wholley, David (FNIH) [T]
Sent: Wed, 6 Dec 2017 22:47:12 +0000
To: Volkow, Nora (NIH/NIDA) [E];Collins, Francis (NIH/OD) [E];Chin, Bill (Chin@phrma.org);Baker, Rebecca (NIH/OD) [E];Wolinetz, Carrie (NIH/OD) [E];Tabak, Lawrence (NIH/OD) [E];Koroshetz, Walter (NIH/NINDS) [E]
Cc: Biarnes, Michael (FNIH) [T];Menetski, Joseph (FNIH) [T]
Subject: FW: Update on Pre-population of the Program survey
Attachments: Survey data collection table.xlsx

Just a quick interim heads up on work done and where it stands...

From: Menetski, Joseph (FNIH) [T]
Sent: Wednesday, December 6, 2017 4:05 PM
To: Wholley, David (FNIH) [T] <dwholley@fnih.org>
Cc: Biarnes, Michael (FNIH) [T] <mbiarnes@fnih.org>; Menetski, Joseph (FNIH) [T] <jmenetski@fnih.org>
Subject: Update on Pre-population of the Program survey

Dear David,

I have been working on pre-populating the survey with the fields from Pain Programs that are active now, or have been active in the last 10 years. In filling out the survey fields, I have made a couple observations.

1. The Survey is 2935 rows long with pre-populated data. I have included all programs that were in any stage of development of the past 10 years, as requested by the team. The data can be sorted by highest level of development observed in the database.
2. There are several fields in the survey that seem to be focused on Study-level data. I have generated a table of the fields in the survey to highlight my concern (Attached to this email). In addition, I have added to that table, which fields are prepopulated, which can be populated with some hands-on effort and which can only be filled in with input from the company developing the drug.

I think this information may be of interest to the teams involved.

Best regards,

Joe

We've moved! Please find our new address below.

Joseph P. Menetski, Ph.D.

Deputy Director of Research Partnerships

Foundation for the National Institutes of Health

(301) 594-6596

fnih.org

11400 Rockville Pike Suite 600 North Bethesda MD 20852

*The FNIH is the #1 ranked biomedical research charitable organization & earned a 4-star rating from
Charity Navigator.*

(b) (5)

NIH - 003469

From: Wholley, David (FNIH) [T]
Sent: Tue, 10 Oct 2017 16:34:48 +0000
To: Collins, Francis (NIH/OD) [E];Myles, Renate (NIH/OD) [E];Tabak, Lawrence (NIH/OD) [E];Lowy, Douglas (NIH/NCI) [E];Doroshow, James (NIH/NCI) [E];Baker, Rebecca (NIH/OD) [E];Wolinetz, Carrie (NIH/OD) [E]
Cc: Adam, Stacey (FNIH) [T];Burklow, John (NIH/OD) [E]
Subject: Gilead

Sent from my BlackBerry 10 smartphone.

From: Wholley, David (FNIH) [T]
Sent: Tue, 10 Oct 2017 17:05:51 +0000
To: Collins, Francis (NIH/OD) [E];Tabak, Lawrence (NIH/OD) [E];Lowy, Douglas (NIH/NCI) [E];Wolinetz, Carrie (NIH/OD) [E];Baker, Rebecca (NIH/OD) [E];Myles, Renate (NIH/OD) [E]
Cc: Adam, Stacey (FNIH) [T];Burklow, John (NIH/OD) [E]
Subject: Gilead

Dear All:

Looks like we have some more work for Renate (sorry about that!) Gilead called me this morning to let me know they are joining PACT. Maria Freire had spoken about PACT with Steve Paul, our Board Chairman, and it turns out Steve had recently met Gilead's CEO, John Milligan, at a venture meeting. Steve emailed John, and I followed that up with Chuck Clapton, their government relations representative, at the Friends of Cancer Research meeting last Wednesday evening. This is new territory for Gilead, by the way, as they have not been involved in many partnerships of this kind. No doubt Gilead's purchase of Kite Pharma in August played a big role in rekindling their interest in PACT.

Renate, given the timing the most likely participant in Thursday's meeting will be Kacy Hutchison, their VP North America Government Relations, but she will confirm that this afternoon and is also getting me the name of a communications contact.

So we now have eleven companies, and just really need to hear back definitively from (b) (4)
Thanks, David

David Wholley
Director, Research Partnerships
Foundation for the National Institutes of Health
(301) 594-6343
fnih.org

Learn more about the FNIH in our 2016 Annual Report: fnih.org/AnnualReport.

From: Wholley, David (FNIH) [T]
Sent: Mon, 13 Nov 2017 03:03:13 +0000
To: Collins, Francis (NIH/OD) [E];Koroshetz, Walter (NIH/NINDS) [E];Porter, Linda (NIH/NINDS) [E];Volkow, Nora (NIH/NIDA) [E];Baker, Rebecca (NIH/OD) [E];Wolinetz, Carrie (NIH/OD) [E];Stein, Jack (NIH/NIDA) [E];Chin, Bill (Chin@phrma.org);Austin, Christopher (NIH/NCATS) [E]
Cc: Biarnes, Michael (FNIH) [T]
Subject: Had another conversation with Chris Flores on Friday afternoon

Dear All:

(b) (5)
(b) (5)

Thanks, David

We've moved! Please find our new address below.

David Wholley
Director, Research Partnerships
Foundation for the National Institutes of Health
(301) 594-6343
fnih.org

11400 Rockville Pike Suite 600 North Bethesda, MD 20852

Learn more about the FNIH in our 2016 Annual Report: fnih.org/AnnualReport.

From: Wholley, David (FNIH) [T]
Sent: Fri, 7 Apr 2017 14:18:34 -0400
To: Collins, Francis (NIH/OD) [E]
Subject: IMI-AMP interactions question you asked
Attachments: IMI-AMP interactions April 2017.pptx

Hi, Francis. If you'll recall [REDACTED] (b) (4) also asked about this on the AMP EEC call last June. In August we provided the EEC with a brief deck (3 slides) outlining the interactions. I have consulted with my folks and updated the slides (underlined text is what's new since August). [REDACTED] (b) (5)
[REDACTED] (b) (5)

(b) (5) We are committed to continuing the dialogue however on at least an annual basis.

Hope that helps!

From: Wholley, David (FNIH) [T]
Sent: Mon, 10 Apr 2017 21:07:22 -0400
To: Stoffels, Paul [JJCUS]
Cc: Melencio, Cheryl (FNIH) [T];Azanell2@its.jnj.com
Subject: Introductory materials for AMP EC
Attachments: 2017_02_24_AMP EC teleconference draft final clean.docx, 2016_12_16_AMP EEC teleconference draft (003) final clean.pdf, AMP EC Slides February 24-FINAL.pdf, AMP Ext EC Slides Dec 16 2016 FINAL.pdf

Dear Paul:

I understand you met with Francis Collins over the weekend and have confirmed your decision to join the AMP Executive Committee. We're really excited to have you on board! As discussed with Francis, here are the slides and minutes from our last EC meeting in February, and from our last Extended EC meeting in December, to assist in your orientation to the Committee. Please let me know if you have any further questions.

Regards,
David Wholley

Foundation for the National Institutes of Health (FNIH)
Accelerating Medicines Partnership (AMP)
Extended Executive Committee (EEC)
Teleconference Meeting Minutes

Friday, February 24, 2017
7:00 – 8:00 a.m. EST

Participants

Neil Buckholtz (NIH/NIA), Rosa Canet-Avilés (FNIH), Bob Carter (NIH/NIAMS), Francis Collins (NIH), Francis Cuss (Bristol-Myers Squibb), Michael Decker (AbbVie), Mikael Dolsten (Pfizer), Ellen Gadbois (NIH), Richard Hodes (NIH/NIA), Marty Hodge (Pfizer), Steve Hoffmann (FNIH), Stephen Katz (NIH/NIAMS), Walter Koroshetz (NIH/NINDS), Allison Lea (NIH), Joseph Menetski (FNIH), Dina Paltoo (NIH), Griffin Rodgers (NIH/NIDDK), Laurie Ryan (NIH/NIA), Susana Serrate-Sztein (NIH/NIAMS), Philip Smith (NIH/NIDDK), Nicole Spear (FNIH), Margaret Sutherland (NIH/NINDS), Larry Tabak (NIH), Melissa Thomas (Lilly), David Wholley (FNIH)

(b) (4), (b) (5)

**Foundation for the National Institutes of Health (FNIH)
Accelerating Medicines Partnership (AMP)
Extended Executive Committee (EEC)
Teleconference Meeting Minutes**

Friday, December 16, 2016

8:00 – 9:30 a.m. EST

Participants

Salvatore Alesci (Takeda), Neil Buckholtz (NIH/NIA), Rosa Canet-Avilés (FNIH), Lon Cardon (GSK), Bob Carter (NIH/NIAMS), Francis Collins (NIH), Mary Collins (Lupus Research Alliance), Francis Cuss (Bristol-Myers Squibb), Michael Decker (Abbvie), Mikael Dolsten (Pfizer), Ellen Goldmuntz (NIH/NIAID), James Hendrix (Alzheimer's Association), Richard Hodes (NIH/NIA), Marty Hodge (Pfizer), Steve Hoffmann (FNIH), Stephen Katz (NIH/NIAMS), Walter Koroshetz (NIH/NINDS), Allison Lea (NIH), James List (Janssen), Jan Lundberg (Lilly), Joseph Miletich (Merck), Amanda Niskar (Arthritis Foundation), Griffin Rodgers (NIH/NIDDK), Laurie Ryan (NIH/NIA), Philip Smith (NIH/NIDDK), Nicole Spear (FNIH), Susana Serrate-Sztein (NIH/NIAMS), Margaret Sutherland (NIH/NINDS), Larry Tabak (NIH), Melissa Thomas (Lilly), Janet Woodcock (FDA), Frank Nestle (Sanofi), Philip Larson (Sanofi), Terry Tarrant (Rheumatology Research Foundation)

(b) (4), (b) (5)

Accelerating Medicines Partnership

Executive Committee Update

24 February, 2017



NIH - 003



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Accelerating Medicines Partnership AMP Parkinson's Disease (Program Development Update)



Foundation for the
National Institutes of Health

NIH - 003492



Accelerating Medicines Partnership

Type 2 Diabetes



Foundation for the
National Institutes of Health

NIH - 003495



Accelerating Medicines Partnership

RA/SLE



Foundation for the
National Institutes of Health

NIH - 003505



Accelerating Medicines Partnership

Alzheimer's Disease



FNIH
Foundation for the
National Institutes of Health

NIH - 003515



Upcoming EC meetings

■ Next Meeting

- AMP EC: Friday, May 5 from 7:00 am – 8:00 am

Appendix

NIH - 003523

Accelerating Medicines Partnership

Extended Executive Committee Update #6

16 December, 2016



NIH - 003



Accelerating Medicines Partnership

RA/SLE

(b) (4)

Bob Carter, NIAMS



NIH - 003549



Accelerating Medicines Partnership

Alzheimer's Disease

Laurie Ryan, NIA

(b) (4)



NIH - 003558



Accelerating Medicines Partnership

Type 2 Diabetes

Phil Smith, NIDDK

(b) (4)



FNIH

Foundation for the
National Institutes of Health

NIH - 003568



Accelerating Medicines Partnership AMP Parkinson's Disease (Program Development Update)

Walter Koroshetz, NINDS
David Wholley, FNIH



NIH - 003577



Extended Executive Committee

■ Next Meeting:

- AMP Extended Executive Committee: June 30, 2017 from 7:00am – 8:30 am Eastern US Time

From: Wholley, David (FNIH) [T]
Sent: Fri, 6 Oct 2017 20:44:44 +0000
To: Baker, Rebecca (NIH/OD) [E];Collins, Francis (NIH/OD) [E]
Subject: Just entered tunnel as you called on me

Should be about 3 mins
Sent from my BlackBerry 10 smartphone.

From: Wholley, David (FNIH) [T]
Sent: Wed, 11 Oct 2017 18:59:42 +0000
To: Myles, Renate (NIH/OD) [E]
Cc: Collins, Francis (NIH/OD) [E]
Subject: (b) (4), (b) (6)
Importance: High

(b) (4)



Please let me know if I may be of further assistance. David

David Wholley
Director, Research Partnerships
Foundation for the National Institutes of Health
(301) 594-6343
fnih.org

Learn more about the FNIH in our 2016 Annual Report: fnih.org/AnnualReport.

From: Wholley, David (FNIH) [T]
Sent: Wed, 31 May 2017 18:45:46 -0400
To: Collins, Francis (NIH/OD) [E]
Cc: Canet-Aviles, Rosa (FNIH) [T];Vardanian, Lilit (FNIH) [T];Melencio, Cheryl (FNIH) [T];Wood, Gretchen (NIH/OD) [E];Di Mantova, Emma (NIH/OD) [E];Boskent, Celeste (NIH/OD) [E];NIHDirectorMeetings;Gadbois, Ellen (NIH/OD) [E];Lea, Allison (NIH/OD) [E];Tabak, Lawrence (NIH/OD) [E]
Subject: Materials for AMP EC Pre-Call tomorrow AM
Attachments: AMP EC Slides June 12-DRAFT.pptx, AMP functional validation proposal and responses 5-31-17.docx, 2017_02_24_AMP EC teleconference draft final clean.docx, AMP EC June 12 Attendees.xlsx
Importance: High

Francis:

Here are the materials for tomorrow's (early) morning AMP EC pre-call:

- Draft meeting slides
- Minutes from Feb. 27 meeting
- Latest attendee roster (attendance overall looks promising)

I have also just finalized a summary document containing the collated responses from the three existing AMP programs [REDACTED] (b) (5) validation proposal. Much of the text appears individually in the AMP EC slides, however the document contains some additional text. I would appreciate you taking a look at it before we send it to the other EC members.

I apologize for the unusually late timing on sending these: tomorrow's pre-call is a little in advance of when we usually do these, so there were more than usual late additions to the slides, in addition to the need to incorporate comments on [REDACTED] (b) (5) response document.

Thanks,
David

Accelerating Medicines PartnershipExecutive Committee Update

12 June, 2017



NIH - 003



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(b) (5)

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Accelerating Medicines PartnershipAMP Parkinson's Disease (Program Development Update)



NIH - 003591



Accelerating Medicines PartnershipType 2 Diabetes



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Accelerating Medicines PartnershipRA/SLE



Foundation for the
National Institutes of Health

NIH - 003605



Accelerating Medicines Partnership

Alzheimer's Disease



FNIH

Foundation for the
National Institutes of Health

NIH - 003614



Upcoming EC meetings

- **Next MeetingAMP EEC: Friday, June 30 from 7:00 am – 8:30 amAMP EC: Friday, August 25 from 7:00 am – 8:00 am**

Foundation for the National Institutes of Health (FNIH)
Accelerating Medicines Partnership (AMP)
Extended Executive Committee (EEC)
Teleconference Meeting Minutes

Friday, February 24, 2017
7:00 – 8:00 a.m. EST

Participants

Neil Buckholtz (NIH/NIA), Rosa Canet-Avilés (FNIH), Bob Carter (NIH/NIAMS), Francis Collins (NIH), Francis Cuss (Bristol-Myers Squibb), Michael Decker (AbbVie), Mikael Dolsten (Pfizer), Ellen Gadbois (NIH), Richard Hodes (NIH/NIA), Marty Hodge (Pfizer), Steve Hoffmann (FNIH), Stephen Katz (NIH/NIAMS), Walter Koroshetz (NIH/NINDS), Allison Lea (NIH), Joseph Menetski (FNIH), Dina Paltoo (NIH), Griffin Rodgers (NIH/NIDDK), Laurie Ryan (NIH/NIA), Susana Serrate-Sztein (NIH/NIAMS), Philip Smith (NIH/NIDDK), Nicole Spear (FNIH), Margaret Sutherland (NIH/NINDS), Larry Tabak (NIH), Melissa Thomas (Lilly), David Wholley (FNIH)

(b) (4), (b) (5)

AMP EC June 12 2017		
Name	Attendance	Response
Melencio, Cheryl (FNIH) [T]	Meeting Organizer	None
Buckholtz, Neil (NIH/NIA) [C]	Required Attendee	Accepted
Canet-Aviles, Rosa (FNIH) [T]	Required Attendee	Accepted
Carter, Robert (NIH/NIAMS) [E]	Required Attendee	Accepted
Collins, Francis (NIH/OD) [E]	Required Attendee	Accepted
Decker, Mike	Required Attendee	Accepted-- (b) (6), limited internet access for slides
Dolsten, Mikael	Required Attendee	Accepted
Gadbois, Ellen (NIH/OD) [E]	Required Attendee	Accepted
Hodes, Richard (NIH/NIA) [E]	Required Attendee	Accepted
Hodge, Martin	Required Attendee	Tentative
Hoffmann, Steve (FNIH) [T]	Required Attendee	Accepted
Katz, Stephen I. (NIH/NIAMS) [E]	Required Attendee	Accepted
Koroshetz, Walter (NIH/NINDS) [E]	Required Attendee	Accepted
Lea, Allison (NIH/OD) [E]	Required Attendee	Accepted
Lifton, Richard	Required Attendee	Accepted
Lundberg, Jan	Required Attendee	Accepted
Paltoo, Dina (NIH/OD) [E]	Required Attendee	Accepted
Rodgers, Griffin (NIH/NIDDK) [E]	Required Attendee	Accepted
Ryan, Laurie (NIH/NIA) [E]	Required Attendee	Accepted
Serrate-Sztein, Susana (NIH/NIAMS) [E]	Required Attendee	None
Smith, Philip (NIH/NIDDK) [E]	Required Attendee	Accepted --- but in San Diego and it is 4 a.m. there - will try
Sutherland, Margaret (NIH/NINDS) [E]	Required Attendee	Accepted
Tabak, Lawrence (NIH/OD) [E]	Required Attendee	None
Terry, Sharon MA	Required Attendee	Most likely not, but will try
Vardanian, Lilit	Required Attendee	Accepted
Wholley, David (FNIH) [T]	Required Attendee	Accepted
Sherry Grabus (Science Writer)	Required Attendee	Accepted

From: Melencio, Cheryl (FNIH) [T] on behalf of Wholley, David (FNIH) [T]
Sent: Wed, 22 Feb 2017 09:31:12 -0500
To: Buckholtz, Neil (NIH/NIA) [C];Canet-Aviles, Rosa (FNIH) [T];Carter, Robert (NIH/NIAMS) [E];Collins, Francis (NIH/OD) [E];Cuss, Francis;Decker, Mike;Dolsten, Mikael;Gadbois, Ellen (NIH/OD) [E];Sheri Grabus;Hodes, Richard (NIH/NIA) [E];Hodge, Martin;Hoffmann, Steve (FNIH) [T];Katz, Stephen I. (NIH/NIAMS) [E];tkerere@iqsolutions.com;Koroshetz, Walter (NIH/NINDS) [E];Lea, Allison (NIH/OD) [E];Lifton, Richard;Lundberg, Jan;Jennifer McCulley;Menetski, Joseph (FNIH) [T];Paltoo, Dina (NIH/OD) [E];Rodgers, Griffin (NIH/NIDDK) [E];Ryan, Laurie (NIH/NIA) [E];Serrate-Sztein, Susana (NIH/NIAMS) [E];Smith, Philip (NIH/NIDDK) [E];Spear, Nicole (FNIH) [T];Sutherland, Margaret (NIH/NINDS) [E];Tabak, Lawrence (NIH/OD) [E];Terry, Sharon MA;Thomas, Melissa;Wholley, David (FNIH) [T]
Cc: Boskent, Celeste (NIH/OD) [E];Bronson, Charlette (NIH/NIA) [E];Burrus-Shaw, Cyndi (NIH/OD) [E];Clark, Katie;Craver, Stephanie (NIH/NIAMS) [E];Dowell, Greta (NIH/OD) [E];Edmonds, Pamela;Yuliya Ilchyk;McManus, Ayanna (NIH/OD) [E];Melencio, Cheryl (FNIH) [T];Meltzer, Sherry (NIH/NIAMS) [E];Morgan, Emily (FNIH) [T];Tanya Murza;NIHDirectorMeetings;Poniente, Josefina;Poole, Charlene (NIH/NIDDK) [C];Protasiewicz, Ann;Schulke, Hilda (NIH/NIDA) [E];Sheehan, Joan (NIH/NIA) [E];Walker, Paula (NIH/NINDS) [E];Wood, Gretchen (NIH/OD) [E];Zander, Debra
Subject: Materials for AMP Executive Committee February 24 Teleconference
Attachments: AMP EC Slides February 24-FINAL.pdf, 2016-11-18_AMP_EC_Telecon_minutes_RLA Final draft.pdf, 2016_12_16_AMP EEC teleconference draft (003) final clean.pdf

Dear All:

Please find attached the slides for our AMP EC teleconference this coming Friday morning, February 24 at 7:00 AM Eastern U.S. Time. I have also attached the meeting minutes from our last EC call on November 18 as well as the Extended EC call on December 16.

PLEASE NOTE: We will only have a "quorum" of industry EC members for the first 45 minutes of the call, so we ask that you please keep your presentations on each disease area to no more than 10 minutes each, to allow time for questions. Thanks, and look forward to your participation on the call.

Regards,
David Wholley

Accelerating Medicines Partnership

Executive Committee Update

24 February, 2017



NIH - 003



Contents

(b) (5)

NIH - 003638

Accelerating Medicines Partnership

AMP Parkinson's Disease

(Program Development Update)



Foundation for the
National Institutes of Health

NIH - 003640



Accelerating Medicines Partnership

Type 2 Diabetes



Foundation for the
National Institutes of Health

NIH - 003643



Accelerating Medicines Partnership

RA/SLE



Foundation for the
National Institutes of Health

NIH - 003653



Accelerating Medicines Partnership

Alzheimer's Disease



FNIH
Foundation for the
National Institutes of Health

NIH - 003663



Upcoming EC meetings

■ Next Meeting

- AMP EC: Friday, May 5 from 7:00 am – 8:00 am

Appendix

Appendix

NIH - 003671

**Foundation for the National Institutes of Health
Accelerating Medicines Partnership
Core Executive Committee
Teleconference Meeting Minutes
Friday, November 18, 2016
7:00 a.m.– 8:00 a.m. ET**

PARTICIPANTS

Neil Buckholtz (NIH/NIA), Rosa Canet-Aviles (FNIH), Robert Carter (NIH/NIAMS), Francis Collins (NIH/OD), Francis Cuss (BMS), Michael Decker (AbbVie), Michael Dolsten (Pfizer), Ellen Gadbois (NIH/OD), Richard Hodes (NIH/NIA), Marty Hodge (Pfizer), Steve Hoffmann (FNIH), Steve Katz (NIH/NIAMS), Walter Koroshetz (NIH/NINDS), Allison Lea (NIH/OD), Jan Lundberg (Lilly), Dina Paltsoo (NIH/OD), Griffin Rodgers (NIH/NIDDK), Laurie Ryan (NIH/NIA), Susana Serrate-Sztein (NIH/NIAMS), Philip Smith (NIH/NIDDK), Nicole Spear (FNIH), Margaret Sutherland (NINDS), Lawrence Tabak (NIH/OD), David Wholley (FNIH)

(b) (4), (b) (5)

**Foundation for the National Institutes of Health (FNIH)
Accelerating Medicines Partnership (AMP)
Extended Executive Committee (EEC)
Teleconference Meeting Minutes**

Friday, December 16, 2016

8:00 – 9:30 a.m. EST

Participants

Salvatore Alesci (Takeda), Neil Buckholtz (NIH/NIA), Rosa Canet-Avilés (FNIH), Lon Cardon (GSK), Bob Carter (NIH/NIAMS), Francis Collins (NIH), Mary Collins (Lupus Research Alliance), Francis Cuss (Bristol-Myers Squibb), Michael Decker (Abbvie), Mikael Dolsten (Pfizer), Ellen Goldmuntz (NIH/NIAID), James Hendrix (Alzheimer's Association), Richard Hodes (NIH/NIA), Marty Hodge (Pfizer), Steve Hoffmann (FNIH), Stephen Katz (NIH/NIAMS), Walter Koroshetz (NIH/NINDS), Allison Lea (NIH), James List (Janssen), Jan Lundberg (Lilly), Joseph Miletich (Merck), Amanda Niskar (Arthritis Foundation), Griffin Rodgers (NIH/NIDDK), Laurie Ryan (NIH/NIA), Philip Smith (NIH/NIDDK), Nicole Spear (FNIH), Susana Serrate-Sztein (NIH/NIAMS), Margaret Sutherland (NIH/NINDS), Larry Tabak (NIH), Melissa Thomas (Lilly), Janet Woodcock (FDA), Frank Nestle (Sanofi), Philip Larson (Sanofi), Terry Tarrant (Rheumatology Research Foundation)

(b) (4), (b) (5)

From: Wholley, David (FNIH) [T]
Sent: Fri, 9 Jun 2017 09:31:42 -0400
To: Melencio, Cheryl (FNIH) [T];Buckholtz, Neil (NIH/NIA) [C];Canet-Aviles, Rosa (FNIH) [T];Carter, Robert (NIH/NIAMS) [E];Collins, Francis (NIH/OD) [E];Decker, Mike;Dolsten, Mikael;Gadbois, Ellen (NIH/OD) [E];Hodes, Richard (NIH/NIA) [E];Hodge, Martin;Hoffmann, Steve (FNIH) [T];Hudson, Kathy (NIH/NLM) [V];Katz, Stephen I. (NIH/NIAMS) [E];Koroshetz, Walter (NIH/NINDS) [E];Lea, Allison (NIH/OD) [E];Lifton, Richard;Lundberg, Jan;Paltoo, Dina (NIH/OD) [E];Rodgers, Griffin (NIH/NIDDK) [E];Ryan, Laurie (NIH/NIA) [E];Serrate-Sztein, Susana (NIH/NIAMS) [E];Smith, Philip (NIH/NIDDK) [E];Sutherland, Margaret (NIH/NINDS) [E];Tabak, Lawrence (NIH/OD) [E];Terry, Sharon MA;Jennifer McCulley;Sheri Grabus;Menetski, Joseph (FNIH) [T];tkerere@iqsolutions.com;Thomas, Melissa;Stoffels, Paul;Zanellato, Ann
Cc: Boskent, Celeste (NIH/OD) [E];Bronson, Charlette (NIH/NIA) [E];Burrus-Shaw, Cyndi (NIH/OD) [E];Clark, Katie;Craver, Stephanie (NIH/NIAMS) [E];Doswell, Greta (NIH/OD) [E];Edmonds, Pamela;Yuliya Ilchyk;McManus, Ayanna (NIH/OD) [E];Meltzer, Sherry (NIH/NIAMS) [E];Morgan, Emily (FNIH) [T];Tanya Murza;NIHDirectorMeetings;Poniente, Josefina;Poole, Charlene (NIH/NIDDK) [C];Protasiewicz, Ann;Schulke, Hilda (NIH/NIDA) [E];Sheehan, Joan (NIH/NIA) [E];Simon, Dina (NIH/OD) [C];Walker, Paula (NIH/NINDS) [E];Wood, Gretchen (NIH/OD) [E];Melencio, Cheryl (FNIH) [T]
Subject: Materials for AMP Executive Committee Telecon Monday June 12
Attachments: AMP EC Slides June 12-FINAL.pptx, AMP functional validation proposal and responses 5-31-17.docx, 2017_02_24_AMP EC teleconference draft final clean.docx

Dear AMP Executive Committee Members and Steering Committee Co-chairs:

Please see attached the materials for our AMP Executive Committee call **this coming Monday morning, June 12 at 7:00 AM Eastern time**:

- 1) The PowerPoint slide deck for the meeting, which includes the agenda.
- 2) A Word document containing the collated discussion points from each of the

(b) (5)

(b) (5) Thanks to all the co-Chairs for their efforts in putting this together.

- 3) The minutes from our last AMP EC teleconference, on February 27.

Please let me or Cheryl Melencio know of any issues. We look forward to a productive discussion.

Regards,
David Wholley



NIH - 003703

Accelerating Medicines PartnershipExecutive Committee Update

12 June, 2017



NIH - 003



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Accelerating Medicines PartnershipParkinson's DiseaseProgram Development



FNIH

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Accelerating Medicines Partnership

Alzheimer's Disease



FNIH

Foundation for the
National Institutes of Health

NIH - 003712



Accelerating Medicines Partnership Type 2 Diabetes

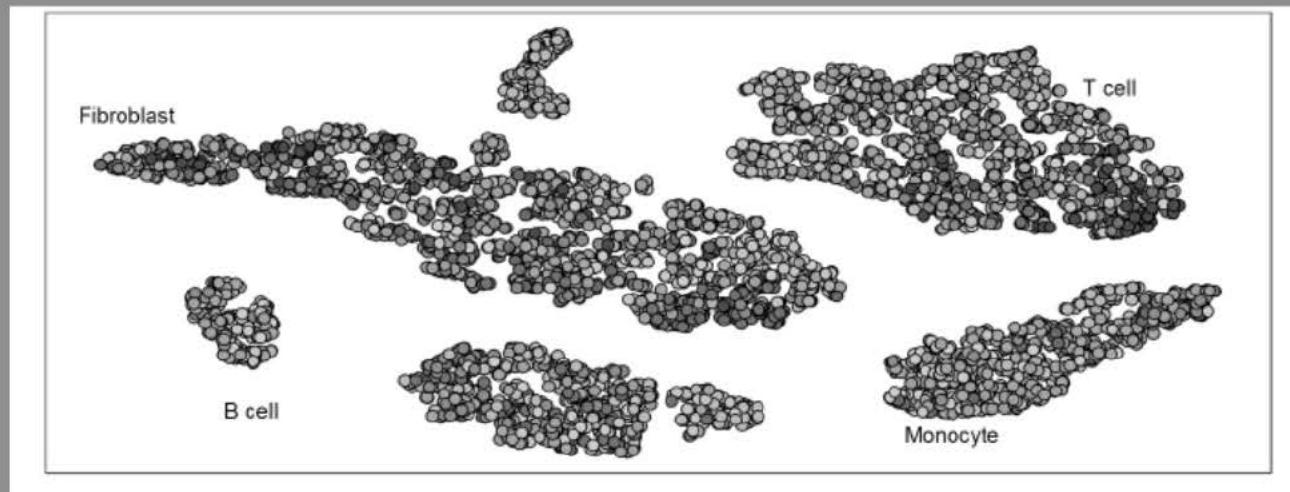


Foundation for the
National Institutes of Health

NIH - 003721



Accelerating Medicines PartnershipRA/SLE



Upcoming EC meetings

- **Next MeetingAMP EEC: Friday, June 30 from 7:00 am – 8:30 amAMP EC: Friday, August 25 from 7:00 am – 8:00 am**

Foundation for the National Institutes of Health (FNIH)
Accelerating Medicines Partnership (AMP)
Extended Executive Committee (EEC)
Teleconference Meeting Minutes

Friday, February 24, 2017
7:00 – 8:00 a.m. EST

Participants

Neil Buckholtz (NIH/NIA), Rosa Canet-Avilés (FNIH), Bob Carter (NIH/NIAMS), Francis Collins (NIH), Francis Cuss (Bristol-Myers Squibb), Michael Decker (AbbVie), Mikael Dolsten (Pfizer), Ellen Gadbois (NIH), Richard Hodes (NIH/NIA), Marty Hodge (Pfizer), Steve Hoffmann (FNIH), Stephen Katz (NIH/NIAMS), Walter Koroshetz (NIH/NINDS), Allison Lea (NIH), Joseph Menetski (FNIH), Dina Paltoo (NIH), Griffin Rodgers (NIH/NIDDK), Laurie Ryan (NIH/NIA), Susana Serrate-Sztein (NIH/NIAMS), Philip Smith (NIH/NIDDK), Nicole Spear (FNIH), Margaret Sutherland (NIH/NINDS), Larry Tabak (NIH), Melissa Thomas (Lilly), David Wholley (FNIH)

(b) (4), (b) (5)

From: Melencio, Cheryl (FNIH) [T] on behalf of Wholley, David (FNIH) [T]
Sent: Thu, 14 Dec 2017 19:14:58 +0000
To: Collins, Francis (NIH/OD) [E];Dolsten, Mikael;Hodes, Richard (NIH/NIA) [E];Katz, Stephen I. (NIH/NIAMS) [E];Koroshetz, Walter (NIH/NINDS) [E];Lifton, Richard;Lundberg, Jan;Rodgers, Griffin (NIH/NIDDK) [E];Stoffels, Paul;Tabak, Lawrence (NIH/OD) [E];Terry, Sharon MA;Wholley, David (FNIH) [T];Carter, Robert (NIH/NIAMS) [E];Collier, David;Fischer, Tanya;Hodge, Martin;Ryan, Laurie (NIH/NIA) [E];Smith, Philip (NIH/NIDDK) [E];Sutherland, Margaret (NIH/NINDS) [E];Thomas, Melissa;Ehlers, Michael;Erion, Mark;Hait, Bill;Lepore, John;Li, Min;Lynch, Thomas;Miletich, Joseph;Moscicki, Rich;Plump, Andrew;Sullivan, Jim;Vessey, Rupert;Woodcock, Janet (FDA/CDER);Zerhouni, Elias;Patrick.Cullinan@Takeda.com;Li, Min;Hargreaves, Richard;Koemeter-Cox, Andrew;Moscicki, Rich;tsherer
Cc: Alesci, Salvatore;Carrillo, Maria;Collins, Mary;Eakin, Guy;Fillit, Howard;Goldmuntz, Ellen (NIH/NIAID) [E];Sheri Grabus;Hanrahan, Leslie;Hargreaves, Richard;Hendrix, James;Lappin, Debra;List, James;Marchiolo, Eryn;Jennifer McCulley;Pragnell, Marlon;Rotrosen, Daniel (NIH/NIAID) [E];tsherer;Tarrant, Teresa;Canet-Aviles, Rosa (FNIH) [T];Gadbois, Ellen (NIH/OD) [E];Sheri Grabus;Hoffmann, Steve (FNIH) [T];Kamphaus, Tania (FNIH) [T];tkerere@iqsolutions.com;Jennifer McCulley;Menetski, Joseph (FNIH) [T];Paltoo, Dina (NIH/OD) [E];Serrate-Sztein, Susana (NIH/NIAMS) [E];Singh, Jyoti (NIH/OD) [E];Vardanian, Lilit (FNIH) [T]
Subject: MATERIALS for AMP Extended Executive Committee Teleconference December 15, 2017
Attachments: AMP Extended EC 12-15-2017 FINAL.pdf, 2017_06_30_AMP EEC teleconference final draft clean.pdf
Importance: Low

Dear AMP Extended Executive Committee members:

Attached are the materials for our call **from 7:00AM to 8:30AM Eastern U.S. Time this Friday, December 15:**

1. An Adobe.pdf document of the slide deck that will be used to guide our discussions during the meeting
2. An Adobe .pdf document containing the draft minutes from our June 30, 2017 AMP EEC call.

Call-in information is contained in the Microsoft Outlook calendar invitation you received for this meeting, but is repeated below. On behalf of the EEC co-chairs, Francis Collins and Mikael Dolsten, I look forward to an efficient and productive discussion.

[Join WebEx meeting](#)

Meeting number (access code): (b) (6)

Meeting password: (b) (6)

Join by phone

(b) (6) Call-in toll number (US/Canada)

Global call-in numbers

[Can't join the meeting?](#)

David Wholley
Director, Research Partnerships
Foundation for the National Institutes of Health
(301) 594-6343
fnih.org

Learn more about the FNIH in our 2016 Annual Report: fnih.org/AnnualReport.

We've moved! Please find our new address below.

Cheryl Melencio
Executive Assistant, Research Partnerships
Foundation for the National Institutes of Health
(301) 402-4970
fnih.org
11400 Rockville Pike Suite 600 North Bethesda, MD 20852

The FNIH is the #1 ranked biomedical research charitable organization & earned a 4-star rating from [Charity Navigator](#).

Accelerating Medicines Partnership

Extended Executive Committee Update #7

15 December 2017



NIH - 003



Accelerating Medicines Partnership

Type 2 Diabetes

Phil Smith, NIDDK

(b) (4)

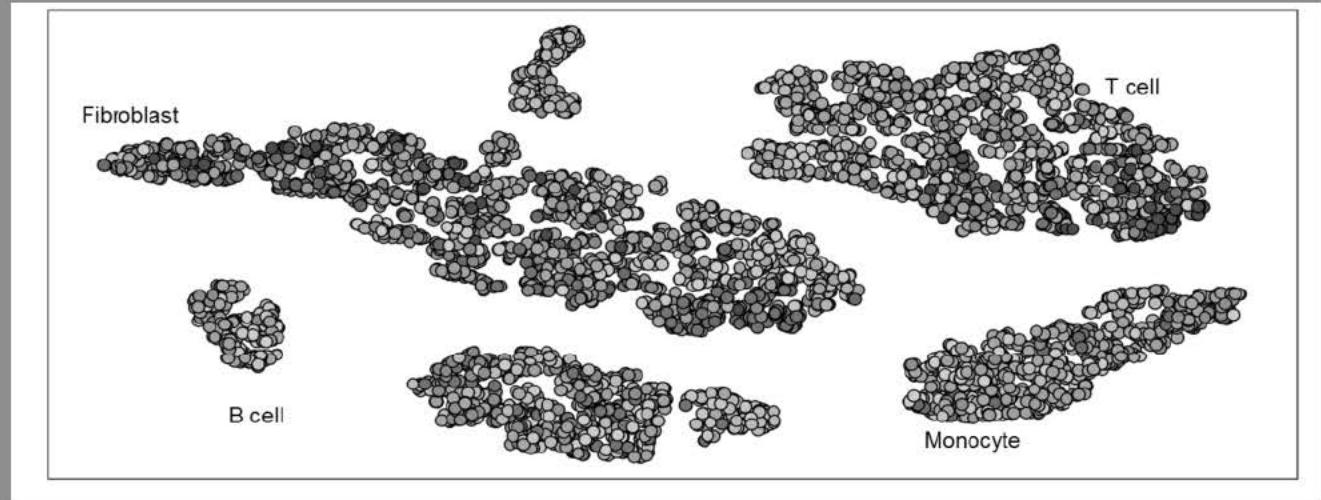


NIH - 003



Accelerating Medicines Partnership

RA/SLE

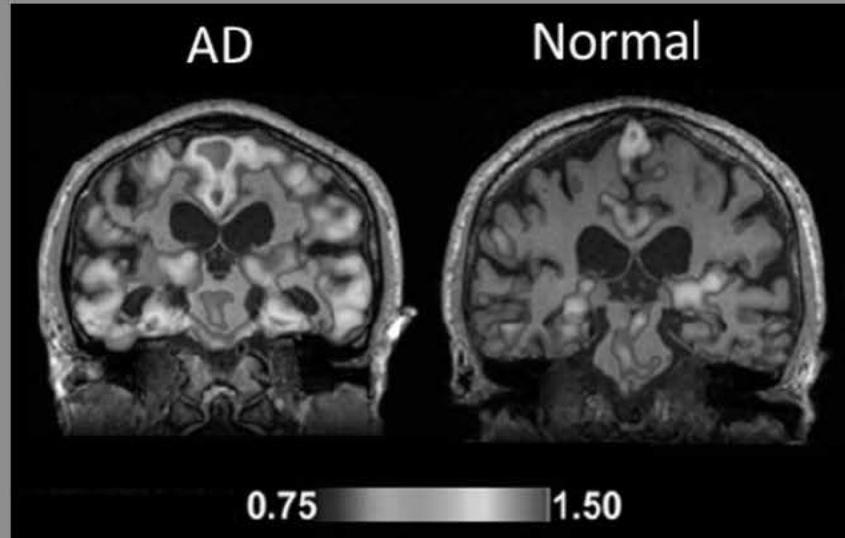


Bob Carter, NIAMS

(b) (4)

Accelerating Medicines Partnership

Alzheimer's Disease



Laurie Ryan, NIA

(b) (4)



NIH - 003792



Accelerating Medicines Partnership

Parkinson's Disease

Program Development

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Marg Sutherland, NINDS



NIH - 003811



Extended Executive Committee

■ Next Meeting:

- AMP Extended Executive Committee: June 29

Backup Slides

NIH - 003820

